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Recent Patents and FDA-Approved Drugs Based on Antiviral Peptides and Other Peptide-Related Antivirals

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Abstract

In spite of existing cases of severe viral infections with a high mortality rate, there are not enough antiviral drugs and vaccines available for the prevention and treatment of such diseases. In addition, the increasing reports of the emergence of viral epidemics highlight, the need for novel molecules with antiviral potential. Antimicrobial peptides (AMPs) with antiviral activity or antiviral peptides (AVPs) have turned into a research hotspot and already show tremendous potential to become pharmaceutically available antiviral medicines. AMPs, a diverse group of bioactive peptides act as a part of our first line of defense against pathogen inactivation. Although most of the currently reported AMPs are either antibacterial or antifungal peptides, the number of antiviral peptides is gradually increasing. Some of the AMPs that are shown as effective antivirals have been deployed against viruses such as influenza A virus, severe acute respiratory syndrome coronavirus (SARS-CoV), HIV, HSV, West Nile Virus (WNV), and other viruses. This review offers an overview of AVPs that have been approved within the past few years and will set out a few of the most essential patents and their usage within the context mentioned above during 2000–2020. Moreover, the present study will explain some of the progress in antiviral drugs based on peptides and peptide-related antivirals.

Keywords Antimicrobial peptide (AMP) · Antiviral peptide (AVP) · Peptidomimetics · Patents

Introduction

Infectious diseases have been recognized by humankind since the very beginning of civilization. Viruses are subvital elements that are considered among the most important human pathogenesis (Saxena et al., 2010). Viruses are known to cause severe infectious diseases with a high mortality rate (Lou et al., 2014; Pour et al. 2019). The 21st century is marked by major epidemics, including ones that even can be considered pandemics, caused by ancient diseases such as cholera, plague, and yellow fever, as well as newer diseases such as severe acute respiratory syndrome (SARS), Ebola, Zika, Middle East Respiratory Syndrome (MERS), HIV (although technically endemic), influenza A (H1N1) pdm/09 and most recently COVID-19 (Ong et al. 2020). Among the mentioned infections, viral infections have attracted more attention due to the high mortality rate of the recent COVID-19 pandemic. Therefore, the discovery and design of antiviral medications seem vital. Antiviral therapeutics can be categorized into three main categories: virucides, immunomodulatory agents, and antivirals. Virucides are agents or physical factors that are capable of neutralizing or destroying a virus; for example, organic solvents, detergents, and ultraviolet light (UV). Immunomodulatory drugs consist of agents that augment the host's response to infections such as antibodies, cytokines, interferons, hormones, antigens, therapeutic vaccines, corticosteroids, and certain neutraceuticals. Antivirals are the molecules that prevent viral proliferation by targeting a particular stage of their life cycles. These drugs might have a limited spectrum of activity, and although may not be as effective on latent viruses, they usually act selectively (Saxena et al. 2009; Saxena et al., 2010).

The uses of antiviral agents are progressing nowadays along with the development of vaccines to effectively

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control viral diseases. The main goals of the antiviral agents are to minimize the inflicted damage to the host cell and eradicate or limit fatal viral diseases. Antiviral drugs, not only penetrate and disrupt the virus, but they can also negatively impact the normal physiological pathways in the host. Antiviral agents also have a narrower therapeutic index when compared to antibacterial drugs. Nephrotoxicity is the primary adverse reaction of antiviral drugs in humans and animals (Bule et al. 2019).

Since the survivability of the virus depends on the host cell, the selection of a target for the design of effective and safe antiviral drugs without harming the host cell is quite a challenging process (Agarwal and Gabrani 2020). In addition, viruses have employed many devious strategies to escape host immune responses and consequently, have been able to plague human health throughout history. Fighting viral infections through vaccines or antiviral drugs or both is always a challenge. Furthermore, discovering and developing new vaccines is normally challenging and time-consuming (Mahmoud, 2016). Even at times when successful strategies are discovered and used, the high rate of genetic change shown by many viruses, especially RNA viruses, often leads to drug resistance or vaccine escape (Blair and Cox 2016). Viruses, including SARS-CoV, SARS-COV2, and influenza, can mutate quickly, as a result, they reduce the efficacy of developed vaccines and targeted antiviral medicines (Anderson and Reiter 2020). Despite the quick progress made in human healthcare, there are just a few virucidal and antiviral therapies that are sufficiently efficient. The increasing reports of the emergence, and re-emergence of viral epidemics (Boas et al., 2019), safety and efficacy limitations and soaring costs, and also the adverse effects of synthetic antiviral drugs, escalate the need to identify new, effective, and safe alternatives to fight viral diseases (Pour et al. 2019).

This article explores one of the promising and emerging fields of ″peptide-based therapeutics″ by namely Antimicrobial peptides (AMPs) against a vast number of microbes i.e., bacteria, fungi, parasites, viruses (Agarwal and Gabrani 2020; Mohan et al., 2010). Over the past several years, a lot of scientific efforts have been made to identify novel and potential peptide-based therapeutics using different advanced technologies. Thus, more than 60 approved peptide drugs are available for sale in the markets of the United States, Europe, Japan, and some Asian countries. Moreover, the number of peptide drugs that are undergoing clinical trials is rising gradually every year. Unfortunately, merely a few therapeutic agents are available for viruses such as human immunodeficiency virus (HIV), hepatitis virus, herpes simplex virus (HSV), and influenza virus (Agarwal and Gabrani 2020). In this review, we will elaborate on some of the progress in peptide and protein-based antiviral drugs focusing on the most important related patents, FDA-approved peptide drugs, and AVPs that are going through the clinical trial phases.

Antivirals Peptides and Other Peptide Related Antivirals

AMPs, a diverse group of bioactive small peptides act as a part of the body's first line of defense against pathogen inactivation. AMPs will be a better choice if employed as an antiviral agent because they occur naturally, and are an innate host defense mechanism (Maiti, 2020). AMPs with antiviral activity or antiviral peptides (AVPs) have turned into a research hotspot and already show tremendous potential to become pharmaceutically available antiviral medicines. AVPs have shown great potential in inhibiting viruses by rupturing the viral capsid, directly inhibiting the virus, and targeting various stages of the viral life cycles (Dutta 2020; Feng et al. 2020; Rider et al. 2011). Some disadvantages of AMPs such as expensive synthesis, time-consuming production, high degradability in some physiological conditions, low stability, immunogenicity, and cytotoxicity have limited their use in the clinic (Kang et al., 2014; Rinanda 2019).

To overcome the above-mentioned limitations, *in silico* approaches are cost-effective strategies to design and modify AMPs (Rinanda 2019). *In silico* study is a logical extension of in vitro method, which simulates biological and physiological processes in a computer (Rinanda 2019). Advanced strategies of rational design together with computational methods are used for the development of more economical and powerful AMPs as potential next-generation antimicrobials (Fjell et al., 2012). The rational design of new drugs has been turned into a major area in medicinal chemistry, aiming at creating pharmaceuticals with greater specificity against microorganisms, together with reduced side effects. In this context, several computational tools are developed to design AMP variants; like empirical methods and machine learning algorithms, as also stochastic approaches. Amongst the machine learning strategies, a particular focus is given to the quantitative structure-activity relationship (QSAR) model, which utilizes physicochemical descriptors to predict the biological activity of peptides from their amino acid sequences (Cardoso et al., 2020).

An example of antiviral peptides that can be designed by the above-mentioned computer-based methods is killer peptides (KPs). Such biologically active peptides subtype, are among a larger group defined as cryptids. The mentioned group can be derived from the proteolytic cleavage of physiological proteins. Cryptids might show a broad spectrum of biological activities, distinct from those of the precursor

proteins. KPs are the leading compounds of a group of antibody-derived fragments vested with various biological activities. KPs have exhibited potent activity against many different viruses such as HIV and influenza, by different action mechanisms (Sala et al., 2018).

The AVPs can be acquired via different approaches: 1- screening of natural sources, 2- design by computational approaches, and 3- high-throughput screening of peptide libraries (Agarwal and Gabrani 2020).

The naturally occurring AVPs are amphipathic and cationic and usually carry a net positive charge (Bulet et al., 2004). It has been proven that hydrophobicity seems to be an effective pattern for many antiviral molecules that target enveloped viruses such as RSVs (Badani et al., 2014). These AVPs can be derived from different sources such as plants, bacteria, animals, and might possess various action mechanisms (Skalickova et al., 2015; Wang, 2012).

Natural antimicrobial peptides have been intensively altered through synthetic chemistry for the purpose of meeting the requirements of potential therapeutic drugs, consequently, increasing the structural diversity more than before (Mojsoska & Jenssen, 2015). Methods are founded based on in vitro display approach, offering genetically encoded peptides with superior quality and high affinity to their targets. Among these methods, phage display, mRNA display, ribosome display, and yeast display are the most common technologies to generate peptides (Linciano et al., 2019; Nevola & Giralt, 2015).

The computer-assisted drug design is based on understanding the structural and functional aspects of the viral machinery. The rational knowledge of the viral proteins and the interactors/cellular partners aids with selecting the target protein. Peptides can be identified computationally; via *in silico* screening through molecular docking. A docking program foresees the target site, usually identified as a pocket or protrusion with hydrogen bond donors and acceptors, hydrophobic characteristics, and different molecular shapes. Next, a peptide library docked with these pockets would give rise to the highest binding peptide (Agarwal and Gabrani 2020; Nevola & Giralt, 2015).

Many online databases are available that contain useful information regarding experimentally tested antiviral peptides. The antiviral peptide database (AVPdp)(Agarwal and Gabrani 2020; Thakur et al., 2012) with 2683 peptides by December 2020 is one of the more important databases (http://crdd.osdd.net/servers/avpdb/index.php).

Many instances of antimicrobial peptides (AMPs) have displayed inhibitory activities against HSV infection. Their antiviral mechanism includes cellular target and viral inactivation (magainin, cecropin, melittin, LL-37, and brevinin-1), interaction with HSV membrane/glycoprotein, and cellular targets excluding heparan sulfate (human and rabbit defensins), viral inactivating effects (tachyplesin and protegrin), bound to gB protein, and blocked HSV-1 attachment (Θ-defensin), and block HSV entry into Vero cells (lactoferrin and lactoferricin) (Hong et al., 2014).

Mucroporin is the first cationic host defense peptide from the scorpion venom *Lychas mucronatus*, which can effectively kill bacteria, especially gram-positive bacteria. The optimized design of mucroporin-M1 by amino acid substitution resulted in the hampering of gram-positive bacteria at low concentrations and increased the hampering of antibiotic-resistant pathogens (Li et al., 2011). Also, mucroporin-M1 exhibited to be virucidal activity against the measles, SARS-CoV, and influenza H5N1 viruses, and it restrained HBV replication in vitro and in vivo (Li et al., 2011; Zhao et al., 2012). Huimin Yan et al. showed that a novel α-helical peptide Hp1090 from scorpion venom can hamper HCV replication and prevents the initiation of HCV infection (Yan et al., 2011).

The design and synthesis of peptide mimics (peptidomimetics) have been developed to mimic the structure, function, and mode of action of host-defense AMPs (Méndez-Samperio, 2014). Many instances of peptidomimetics are reported, most of which were synthesized via altered solid-phase peptide synthesis methods. Some examples of strategies for the production of peptidomimetics include using D-amino acid substitutions, with reduced and functionalized amide bonds, peptoids, urea peptidomimetics, peptide sulfonamides, oligocarbamates, partial or full retro-Inverso peptides, azapeptides, β-peptides, and N-modified peptides. (VanPatten et al. 2020).

Antimicrobial peptidomimetics are superior to AMPs in several aspects, including enhanced stability, cell specificity, enhanced receptor affinity and selectivity, improved bioavailability, better tolerability, and enhanced chemodiversity (Lachowicz et al., 2020; Lenci & Trabocchi, 2020; Méndez-Samperio, 2014). Additionally, the flexibility in the synthesis of these molecules allows fast structure modifications for the creation of novel antimicrobial peptidomimetics, with particular pharmacological properties (Méndez-Samperio, 2014).

Recent Patents in Antiviral Peptides and Other Peptide-Related Antivirals

Simultaneously, with the emergence of studies about the design and fabrication of antiviral peptides and related structures such as peptidomimetics, the patents in this field, fabrication methods, and modification have also been recorded recently. Some most significant patents and their applications in this field during 2000–2020 are introduced in Table 1. These patents presented antiviral activity against

Table 1 Some of the most important patents (2000–2020) in antiviral peptides and peptide-related antivirals

Patent Number*	Patent title	Application	Classification / Peptide type	Sequence	Patent year
US10538554B2	Peptides and uses therefor as antiviral agents	Treatment or prevention of influenza virus infections	Linear peptides containing only normal peptide links having 5 to 11 amino acids/ An isolated peptide	NH2-WWFTFIA-COOH NH2-TWFTFIN-COOH NH2-TKSRFDN-COOH	2020
US10745448B2	Antiviral peptide and use therefor	A synthetic peptide that suppresses growth of vesicular stomatitis virus (VSV)	Cell penetrating peptide (CPP)/ A synthetic peptide	NH2-MLSYLIFALAVSPILGKKRTLRKND RKKR-COOH	2020
US10351604B2	Broad-spectrum anti-infective peptides	Anti-infective peptides that useful against bacteria and viruses	Peptide derivative from Gastrins, Somatostatins and Melanotropins/ / A synthetic peptide	NH2-SGSWLRDVWTWLQSKL-COOH	2019
US9555070B2	Pan-antiviral peptides for protein kinase inhibition	Treatments of cancer, influenza, Tourette's syndrome, pain, and neurological deficits.	Polypeptides derived from alpha-neurotoxin/ Enzyme inhibitors	>AAB25587.1 alpha-neurotoxin, NH2-TKCYKTGDRIISEACPPGQDLCYMK TWCDVFCGTRGRVIELGCTATCPTVKPHEQITCCSTDNCNPHPKMKQ-COOH	2017
US9556237B2	Antiviral rift valley fever virus peptides and methods of use	Treatment or prevention of infection by hemorrhagic fever viruses, such as RVFV, Ebola Virus, and Andes Virus, as well as vesicular stomatitis virus.	Synthetic short peptides based on Rift Valley Fever Virus (RVFV) fusion protein	NH2-WNFFDWFSGLMSWFGGPLK-COOH	2017
RU2575069C2	Biologically active peptides	These peptides are used in an immunomodulation and antiviral pharmaceutical composition.	Synthetic peptides	NH2-HGVSGYGQHGVHG-COOH	2016
RU2576830C2	Biologically active derivatives of alloferon-1	provides stimulating induction of interleukin-18, interferon gamma and inhibition of influenza A and B viruses.	Alloferon-1-derived synthetic peptide	(p-NH_2) –GVSGHGQHGVHG-COOH	2016
US8937154B2	Stabilized therapeutic small helical antiviral peptides	Inhibit HIV assembly and also come up with methods of inhibiting replication of a capsid-containing virus.	Linear peptides containing only normal peptide links having 5 to 11 amino acids/ α-helical peptides	(T/S)FE(D/E)(L/I/W)L(D/Q)YY	2015
US9221874B2	Antiviral peptides against influenza virus	Prevent and treatment of influenza viral infections.	Linear peptides containing only normal peptide links having 12 to 20 amino acids/ peptides having antiviral properties	NH2-RRKKAAVALLPAVLLALLA-COOH NH2-RRKKAVALLPAVLLALLAP-NH_2	2015

Table 1 (continued)

Patent Number*	Patent title	Application	Classification / Peptide type	Sequence	Patent year
EP2462155B1	Novel antipathogenic peptides	These monomeric and multimeric peptidic compounds which have antipathogenic, in particular antiviral and antibacterial activity.	Linear peptides containing only normal peptide links having 12 to 20 amino acids/ monomeric and multimeric peptidic compounds which have antipathogenic	R - V - R - I - K - [K]n - [Q]m K is an amino acid residue with a lysine side chain, or another amino acid residue with a positively charged side chain, Q is an amino acid residue with a glutamine side chain, n is 1 and m is 0 or 1	2015
JP5647111B2	Novel antiviral peptide against avian influenza virus H9N2	These antiviral peptides and fusion phages that act against avian influenza virus (AIV) subtype H9N2	1) An isolated and purified recombinant peptide 2) A synthetic peptide	1) NH2-NDFRRSKT-COOH 2) NH2-CNDFRSKTC-COOH or NH2-NDFRSKKT-COOH	2014
RU2503686C2	New antiviral peptides that prevent binding of virus to dlc8	This patent includes a new antiviral therapy consisting in inhibition of viruses that use a system of dynein by means of counteraction mechanisms, As a result mainly preventing interaction between virus protein and cellular protein DLC8.	Peptides derived from Gastrins, Somatostatins and Melanotropins/ peptide capable of binding to a DLC8 protein	NH2-YTTTVTTQNTASQT-COOH	2014
KR101412077B1	Anti-Tobacco mosaic viral peptide and use thereof	A anti-tobacco mosaic virus peptide	Cyclic peptides containing only normal peptide links	Cyclo (STVMPLSLG)	2014
JP5385497B2	Peptide derivative fusion inhibitor for HIV infection	This patent has presented viral infection inhibitors, exhibit anti-fusion-inducing properties, inhibitory activity against HIV and simian immunodeficiency virus (hereinafter “SIV”)	gp41- derived synthetic peptides	NH2-KFWGWLSAWKDLKQLEYENKEQQ IQAQEILATIKQEWEQW-COOH	2014
US8722616B2	Anti- HIV peptides and methods of use thereof	Treatment of microbial infections More specifically provides anti- HIV peptides.	An isolated peptide discovered based on the Antimicrobial Peptide Database	NH2-LLGDLLRKSKEKIGKEFKRIVGRFKR FRKKFKKLFKKIS-COOH	2014

Table 1 (continued)

Patent Number*	Patent title	Application	Classification / Peptide type	Sequence	Patent year
US8748566B2	Pharmacologically active antiviral peptides and methods of use	The antiviral peptides exhibit activity against a broad spectrum of viruses, including enveloped and non-enveloped viruses.	Linear peptides containing only normal peptide links having 12 to 20 amino acids/ These peptides comprise membrane transiting peptides, and active fragments and derivatives of such peptides.	NH2-RRKKAAVALLPAVLLALLAP-COOH	2014
US8603965B2	Pharmaceutical composition for the prophylaxis and treatment of HIV infection and its use	This invention provides an antivirus peptide and treatment for HIV infection.	Peptides derived from Gastrins, Somatostatins and Melanotropins	NH2-SWETWEREIENYTRQIYRILEESQEQ QDRNERDLLE-COOH	2013
CN1968710B	Stable peptide mimetic of HIV gp41 fusion intermediate	These HIV-derived chimeric peptides may provide for therapeutic treatment against HIV infection by inhibiting the virus-host cell membrane fusion process.	Alpha-helix chimeric peptide	NH2-LLQLTVWGIKQLQARIL-COOH	2013
ES2387827T3	Helical antiviral peptides, small, stabilized therapeutic	These peptides inhibit the assembly of viruses that contain a capsid thus has positive effect on HIV infection treatment.	Linear peptides containing only normal peptide links having 12 to 20 amino acids/ Helical, small-sized, therapeutic and stabilized antiviral peptides in which two of the amino acids are unnatural amino acids that have R or S stoichiometry in the α-carbon	(I / V) (T / S) (F / W / Y) (I / O) (D / E) L (L / D / T) (D / A / S) (Y / F) (Y / M)	2012

Table 1 (continued)

Patent Number*	Patent title	Application	Classification / Peptide type	Sequence	Patent year
ES2392106T3	Chimeric peptide molecules with antiviral properties against viruses of the Flaviviridae family	This patent presented treatment and prevention of infections caused by viruses of the Flaviviridae family.	Hybrid and chimeric peptides	[P] - [L1] - [I] - [L2] - [T] or [I] - [L3] - [P] - [L4] - [T] In which [P] is the amino acid sequence of a "cell penetrator" peptide, typically 10–30 amino acids that has the ability to allow the internalization of the entire peptide molecule in the cell cytoplasm and gain access to the surroundings of the rough endoplasmic reticulum (RER); [L1, L2, L3, L4] are linker sequences of 0–6 residues; [I] is an inhibitory sequence of the activation of the NS3pro protease that contains residues that are in contact with at least one amino acid of the beta chains B2a and B2b of the C-terminal barrel or of the beta A1 chain of the N-terminal barrel of The NS3pro protein of flavivirus (or the structurally corresponding region of hepacivirus or pestivirus) in its active or inactive conformation; [T], amino acid sequence of 0 to 10 residues, which is typically one or two retention signals in the ER (such as the KDEL, KKXX and LRRRRL sequences) or the XRR sequence capable of binding to the substrate binding sites P1 and P2 of the NS3pro protease of flavivirus.	2012
EP1705182B1	Antitumor and antiviral peptides	This peptide has expressed Antitumor, anti-proliferative, cytotoxic, and antiviral properties.	Linear peptides containing only normal peptide links having 12 to 20 amino acids/ a peptide exhibiting antitumor and antiviral properties/ A synthetic peptide	NH2-HGVSGWGQHGTHG-COOH	2012
JP4788958B2	Antiviral peptides and uses thereof	These artificially synthesized antiviral peptide has shown antiviral activity against at least one virus.	Artificially synthesized antiviral peptide	NH2-RQARNRRRRRWR-COOH	2011
US8017579B2	Treatment of viral infections	Treating and preventing the development of viral infections.	An isolated polypeptide or analogue thereof, comprising a tandem repeat of Apo-lipoprotein B	NH2-LRTRKRGRKLRTRKRGRK-COOH	2011
JP4831410B2	Antiviral peptides and antiviral agents	This patent relates to an antiviral agent (composition) mainly composed of an antiviral peptide and a method for producing the same.	A synthetic peptide	NH2-RQARRNRRRRWR-COOH	2011
US7777000B2	Anti-viral activity of cathelicidin peptides	Treatment of dermatitis and viral infections.	Cationic antimicrobial peptides of the cathelicidin family including LL-37, related homologues, and variants thereof	NH2-GLLRKGGEKI-COOH NH2-GEKLKKIGQK-COOH NH2-IKNFFQKLVP QPEQ-COOH	2010

Table 1 (continued)

Patent Number*	Patent title	Application	Classification / Peptide type	Sequence	Patent year
US7691382B2	Antiviral polypeptides comprising tandem repeats of APOE 141–149 and variants thereof	useful for preventing or treating viral infections	An isolated and purified antiviral polypeptide derived from a tandem repeat of apoE141-149	NH2-WRKWRKRWWWRKWRKRWW-COOH	2010
US7790171B1	Antiviral peptides obtained from the tryptophan-rich hydrophobic cluster of the HIV-1 reverse transcriptase	An inhibitor of HIV replication, comprising an antiviral peptide	Peptides derived from Gastrins, Somatostatins and Melanotropins/ inhibitor of the dimerization of reverse transcriptase of the virus	NH2-KETWETWWTE-COOH	2010
JP4463545B2	Long-lasting fusion peptide inhibitors against HIV infection	This patent relates to the treatment of viral infections of HIV, RS virus (RSV), human parainfluenza virus (HPV), measles virus (MeV), and simian immunodeficiency virus (SIV).	Peptides derived from Gastrins, Somatostatins and Melanotropins/ C34 peptide derivatives	NH2-LLEQENKEQQNQSEEILSTYNNIER DWEMW-COOH	2010
US7432045B2	Method of inhibiting influenza infection with antiviral peptides	The antiviral peptides exhibit activity against a broad spectrum of viruses, including enveloped and non-enveloped viruses, and useful for treating viral infections.	Peptides derived from Gastrins, Somatostatins and Melanotropins/ These peptides comprise membrane transiting peptides, and active fragments and derivatives of such peptides.	NH2-RRKKAAVALLPAVLLALLAP-COOH	2008
AU2004240765B2	Modified antiviral peptides with increased activity and cell membrane affinity	This patent relates to compounds with increased antiviral activity, in particular increased anti- HIV activity.	Peptides derived from Gastrins, Somatostatins and Melanotropins/ A synthetic peptide	NH2-RQIKIWFQNRRMKWKK-COOH Antiviral peptide including one of the sequences GPG and RQGY and, bonded to the C-end of the peptide	2008

Table 1 (continued)

Patent Number*	Patent title	Application	Classification / Peptide type	Sequence	Patent year
RU2290197C2	Pharmaceutical agent for treatment of HIV-infection, composition containing thereof and methods for its using	A fusion inhibitor that can be used to treat HIV infection.	Peptides derived from Gastrins, Somatostatins and Melanotropins	NH2-SWETWEREIENYTKQIYKILEESQE QQDRNEKDLLE-COOH	2006
KR100438415B1	Novel antiviral peptide derived from Helicobacter pylori and use thereof	This peptide exhibit excellent virus-cell fusion inhibitory activity and thus can be usefully used as antiviral agents.	A peptide synthesized by substituting an amino-terminal region of ribosomal protein L1 (RPL1) produced by Helicobacter pylori bacteria with other amino acids/ Novel antiviral peptide derived from *Helicobacter pylori*	NH2-AKKVFKRLEKLFSKIQ-COOH	2004

* https://patents.google.com/

various viruses such as HIV, Rift Valley Fever Virus Peptides (RVFV), influenza A, B, and Ebola viruses.

FDA Approved AVPs and Other Peptide Related Antivirals

More than 60 approved peptide drugs are available for selling in the market countries including the United States, Europe, Japan, and some Asian countries. Moreover, the number of peptide drugs undergoing clinical trials is rising slowly year by year. For example, over 400 peptides are under clinical trial phases, more than 150 are in active clinical development, and a further 260 have been tested in human clinical trials. The peptide-based antiviral therapeutics have been confirmed for the human immunodeficiency virus (HIV), Influenza virus, and hepatitis virus (Agarwal and Gabrani 2020; Findlay et al., 2013; Lau & Dunn, 2018).

Enfuvirtide (also known as T-20) is the first FDA-approved viral peptide inhibitor. It is a synthetic peptide with 36 residues that act against HIV. Enfuvirtide prevents the fusion of the HR1 domain to HR2 throughout HIV infection (Lalezari et al., 2003; Matthews et al., 2004; Teissier et al., 2011). The first generation of fusion inhibitors, Enfuvirtide, nSJ-2176, and C34, are peptidomimetics of the HR2 domain and act by competitively binding to HR1 to prevent the interaction among HR-1 and HR-2, consequently blocking the formation of the 6-helix bundle and fusion of HIV-1 along with the extracellular membrane of host cells (Berkhout et al., 2012). Enfuvirtide has minimal systemic toxicity, but long-term use of it leads to the frequent occurrence of painful injection site reactions (Henrich & Kuritzkes, 2013).

Boceprevir and Telaprevir are synthetic peptides against the hepatitis C virus (HCV) and were approved by the FDA in 2011. The peptides act on a protease inhibitor called NS3/4 and interfere with viral replication (De Clercq & Li, 2016; Divyashree et al., 2020).

There are nine peptidomimetic drugs on the market for the treatment of AIDS (Acquired immunodeficiency syndrome), and at least four in clinical development for the treatment of HCV infections (Tsantrizos, 2008).

A peptidomimetic called Saquinavir acts as a protease inhibitor for HIV-1 (De Clercq, 2009b). This molecule carries a hydroxy ethylene scaffold and mimics the typical peptide bond(but unlike the typical peptide bond, it isn't broken by HIV-1 protease) (De Clercq, 2009a).

Recently, with the outbreak of the COVID-19 pandemic, many antiviral peptides and peptidomimetics against SARS-CoV-2 have been reported (Mousavi Maleki et al., 2021). Various therapeutic agents rapidly taken into clinical trials are mainly based on available drugs with non-specific antiviral activities or compounds pharmacologically speculated to be effective in increasing the overall clinical outcome of COVID-19 patients (Mahendran et al., 2020). To date, no peptide antiviral drug for COVID-19 has entered the clinical trial. However, some researchers have recommended some FDA-approved peptide drugs for clinical trials of COVID-19 through virtual screenings and in silico drug repurposing methods. Madanchi et al., in one of these studies, showed that the enfuvirtide could inhibit SARS-CoV2 entry into the host cell with great potency and recommended it for COVID-19 clinical trials (Ahmadi et al., 2022). FDA-approved peptide-like small molecules, amino acid-like derivatives, and peptidomimetics such as remdesivir and lopinavir have been utilized in COVID-19 clinical trials and even in its treatment. The FDA-approved AVPs and other related peptide structures (from https://go.drugbank.com/drugs) are reported in Table 2.

Conclusion

Limitations of available medications for treating the many viral infections, the emergence of problematic resistance to these drugs, and the lack of effective antiviral vaccines against the new mutant strains have led to researchers finding novel and substitute therapeutics. Here, we reported the patents and FDA-approved drugs based on AVPs, peptidomimetics, and peptide-like structures that have good potential for use as new antiviral agents against many viral infections. In this article, some patents in antiviral peptides, peptidomimetics, and FDA-approved peptides have been collected through extensive studies in order to raise awareness of their antiviral potential. Our study showed that many of these peptides and peptidomimetics can be used against emerging viruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2.

Table 2 Category, application and mechanism actions of some FDA approved AVPs, peptidomimetics, peptide-like structures, small molecules and amino acid-like derivatives

Name	Commercial name	Type /category	FDA approved year	Application	Mechanism of action	Reference
Tesamorelin	EGRIFTA	Synthetic peptide/ Receptor binding	November 2010	Treatment of HIV-infected patients with lipodystrophy	Tesamorelin acetate is a synthetic analogue of human hypothalamic Growth Hormone Releasing Factor (hGRF) indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy	(Bedimo 2011; Spooner & Olin, 2012)
Telaprevir	INCIVEK	Synthetic peptide/ Inhibitor	May 2011	Treatment of chronic Hepatitis C Genotype 1	Telaprevir is a NS3/4a protease inhibitor used to inhibit viral HCV replication	(Forestier & Zeuzem, 2012; Kim et al., 2012)
Bulevirtide	Hepcludex	Synthetic peptide	European Union in July 2020	Treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.	Bulevirtide works by attaching to and blocking a receptor (sodium/bile acid cotransporter) through which the hepatitis delta and hepatitis B viruses enter liver cells. By blocking the entry of the virus into the cells, it limits the ability of HDV to replicate and its effects in the body.	http://drugapprovalsint.com/bulevirtide-acetate/#more-10650
Enfuvirtide	Fuzeon	Peptidomimetic/ Entry inhibitor	March 2003	Human Immunodeficiency Virus Type 1 (HIV-1 /AIDS)	Enfuvirtide is a HIV fusion inhibitors, binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral with CD4cellular membranes.	(Greenberg & Cammack, 2004; Matthews et al., 2004)
Peramivir	Rapivab	Peptide like Small molecule (organic Small compounds known as gamma amino acids and derivatives. These are amino acids having a ($-NH_2$) group attached to the gamma carbon atom)/Neuraminidase inhibitors	December 2014	Treatment of acute Type A and B influenza in patients aged ≥ 2 years who have been symptomatic for no more than 2 days	Peramivir is an inhibitor of influenza neuraminidase, preventing new virus particles from leaving infected cells.	(Bantia et al., 2006)
Nelfinavir*	Viracept	Synthetic peptide/ Protease inhibitor	March 1997	Human Immunodeficiency Virus Type 1 (HIV-1) Infection	Nelfinavir inhibits the HIV viral proteinase enzyme which prevents cleavage of the gag-pol polyprotein, resulting in noninfectious, immature viral particles.	(Kaldor et al., 1997)

Table 2 (continued)

Name	Commercial name	Type /category	FDA approved year	Application	Mechanism of action	Reference
Atazanavir	Reyataz and Atazor	Peptidomimetic or Azapeptide (organic compounds known as valine and derivatives)/ Protease inhibitor	June 2003	Human Immunodeficiency Virus Type 1 (HIV-1) Infection	Atazanavir selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells by binding to the active site of HIV-1 protease, thus preventing the formation of mature virions. It blocks the active site of HIV protease to prevent the cleavage of Gag and Gagpol precursor proteins.	(Croom et al., 2009; Le Tiec et al., 2005)
Remdesivir*	Veklury	Peptide like Small molecule (This compound belongs to the class of organic compounds known as alpha amino acid esters. These are ester derivatives of alpha amino acids)/ Inhibitor	May 2020	Novel Coronavirus Infectious Disease (SARS-CoV-2 or COVID-19) Or Treatment of adult and pediatric patients aged 12 years and over weighing at least 40 kg for coronavirus disease 2019(COVID-19)	Remdesivir is a nucleoside analog used to inhibit the action of RNA polymerase Remdesivir is a phosphoramidite prodrug of a 1'-cyano-substituted adenosine nucleotide analogue that competes with ATP for incorporation into newly synthesized viral RNA by the corresponding RdRp complex	(Malin et al. 2020; Sheahan et al. 2017; Warren et al., 2016)
Glecaprevir	Mavyret	Peptide like Small molecule This compound belongs to the class of organic compounds known as cyclic peptides. These are compounds containing a cyclic moiety bearing a peptide backbone. inhibitor	August 2017	Chronic Hepatitis C Genotype1-6	Glecaprevir is an inhibitor of the HCV NS3/4A protease, which is a viral enzyme necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins	(Salam and Akimitsu 2013)
Oseltamivir*	Tamiflu	Synthetic derivative prodrug of ethyl ester /Neuraminidase inhibitors	December 2000	Treatment and prophylaxis of infection with influenza viruses A (including pandemic H1N1) and Influenza B	Oseltamivir is an antiviral neuraminidase inhibitor exerts its antiviral activity by inhibiting the activity of the viral neuraminidase enzyme found on the surface of the virus, which prevents budding from the host cell, viral replication, and infectivity.	(De Jong et al., 2005; Ward et al., 2005)

Table 2 (continued)

Name	Commercial name	Type /category	FDA approved year	Application	Mechanism of action	Reference
Saquinavir	Invirase and Fortovase	Peptidomimetic/ Protease inhibitor	December 2004	Saquinavir is an HIV-1 protease inhibitor used in combination with ritonavir and other antiretrovirals for the Treatment of human immunodeficiency virus-1(HIV-1)	Saquinavir exerts its antiviral activity by inhibiting an enzyme critical for the HIV-1 viral lifecycle	(De Clercq, 2009a, 2009b)
Indinavir	Crixivan	Peptidomimetic Protease inhibitor	March 1996	Antiretroviral drug for the treatment of HIV infection.	Indinavir binds to the protease active site and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature non-infectious viral particles	(Kosel et al., 2003)
Lopinavir*	Kaletra	Peptidomimetic/ Protease inhibitor	September 2000	Treatment of HIV-1 infection in adults and pediatric patients ≥ 14 days old.7	Lopinavir is a protease inhibitor peptidomimetic molecule - it contains a hydroxyethylene scaffold that mimics the peptide linkage typically targeted by the HIV-1 protease enzyme but which itself cannot be cleaved, thus preventing the activity of the HIV-1 protease	(Chan et al., 2015; Chu et al., 2004; De Clercq, 2009a; Niu et al. 2019)
Boceprevir	Victrelis	Peptidomimetic/ Inhibitor	May 2011	Chronic Hepatitis C Genotype 1	Boceprevir is a NS3/4a protease inhibitor used to inhibit viral HCV replication Boceprevir is an inhibitor of NS3/4A, a serine protease enzyme, encoded by HCV genotypes 1 and 4 Synthesis. These enzymes are essential for viral replication and serve to cleave the virally encoded polyprotein into mature proteins like NS4A, NS4B, NS5A and NS5B	(Treitel et al., 2012; Wilby et al. 2012)
Ritonavir	Norvir	Peptidomimetic/ Protease inhibitor	June 1999	Human Immunodeficiency Virus (HIV) Infections	Ritonavir is an HIV protease inhibitor that interferes with the reproductive cycle of HIV Ritonavic inhibits the HIV viral proteinase enzyme that normally cleaves the structural and replicative proteins that arise from major HIV genes, such as gag and pol.	(Hull & Montaner, 2011)

*= Recommended for SARS-COV2

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Declarations

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