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ANTIMICROBIAL PEPTIDES AS POTENT COMPOUNDS FOR REDUCTION OF COVID-19 INFECTION

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COVID-19 is an infectious disease caused by a new identified coronavirus in china, SARS-COV2. There are no efficient treatments for COVID-19. Therefore, it is essential to investigate new therapies for this problem. Due to specific mechanism for inhibition of microbial growth, antimicrobial peptides can be considered as one of the best therapies in this field. Antimicrobial peptides (AMPs) are important agents that are made by the immune system in response to pathogens. This kind of immune response exists in all animal categories from prokaryotes to humans. Different types of AMPs have been identified and isolated from various organisms from bacteria to humans. So far, 190 antiviral peptides with antiviral effects have been extracted and introduced from various animal sources. These natural compounds and their derivatives, e.g. synthetic peptides, can be considered as new therapeutic goals in COVID-19. In this review, we assessed these peptides in different animal categories as well as synthetic peptides and the possibility of using these compounds in the treatment of COVID-19.

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INTRODUCTION

COVID-19 is an infectious disease caused by a new identified coronavirus in china, SARS-COV2[1]. So far, more than three million people have been infected worldwide. There are no efficient treatments for COVID-19[2]. The use of some strategies such as enough rest and drugs to relieve fever, aches, and pains can be helpful. However, previously developed drugs for treatment of other viral infections have been tested for prevention of the virus that causes COVID-19[3]. It is too difficult to develop treatments for viral illnesses such as COVID-19. A new drug must be able to target virus's life cycle with high specificity and inhibit virus without any cytotoxic effect[4]. In innate immune system of all animals, there are antimicrobial peptides (AMPs) with short length that show inhibitory activity on various pathogens[5]. These peptides are used by a wide range of organisms, including mammals, birds, insects, crustaceans, fish, plants and microbes[6&7]. Some of these compounds are made continuously in the body, while others are synthesized only when the body is attacked by microbes. At the time of the microbe's attack, the body's primary defense system increases the synthesis of these compounds to a great extent, and thus the primary barrier to the body acts more efficiently against foreign invasions[8&9]. Research has shown that some of these AMPs, in addition to intrinsic antimicrobial activity, act as immunosuppressive signals and thus contribute to the immune system's activity[10]. AMPs have many of the characteristics of a new class of antibiotics and can be a complementary therapeutic to traditional antibiotics[11]. In addition, it has been shown that these compounds neutralize endotoxins[12]. The best use of these peptides in living organisms is the disposal of lethal microbes from the internal system of the body. With the advent of science, these peptides can be extracted and used as new drug compounds in COVID-19. In this review, we assessed these peptides in different animal categories and the possibility of using these compounds in the treatment of COVID-19.

AMPs with Antiviral Activity

Among 3180 discovered or synthesized AMPs from six kingdoms, 190 peptides have antiviral activity[10]. The highest number of antiviral peptides was obtained from amphibians (Fig. 1). We evaluated the amino acid composition of these identified peptides (Table 1). This evaluation showed that the percentage of glycine, lysine and leucine was higher in all reported peptides and the percentage of amino acids valine, proline, serine, threonin was lower than other amino acids. In comparison with other antimicrobial activities (anti-bacterial, antifungal, and etc.), the presence of basic amino acid (Lysine) is important characteristic of these peptides. Other evaluated properties of these 190 peptides was also summarized in table 1.

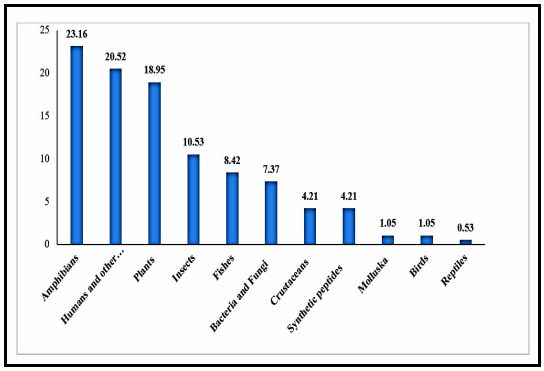

Fig. 1: Frequency distribution of 190 reported antiviral peptides in term of purified source.

Table 1: The frequency of evaluated properties of 190 reported antiviral peptides.

Properties		%
length	Minimum	5
	Maximum	49
	Mean	28.9
Mean Aliphatic index	Positive	75.6
	Negative	24.4
Instability		Less than 40%
Net charge	Positive	68%
	Negative	25%
	Neutral	7%
Hydropathy index	Positive	68.4
	Negative	31.6
Secondary Structure	Alpha helix	48.6
	Beta sheet	18.7
	Coil	8.2
	Unknown	24.5

Antiviral mechanisms of peptides

These peptides can inhibit viral infection by different strategies. The most important proposed strategies are suppressing viral gene expression, Protection of human neutrophils, blocking the entry of the virus through the interaction with cellular receptors, preventing the spread of the virus between cells, preventing the entry of the virus through the interaction with viral glycoproteins, progression of cell death in infected cells, and etc[13].

Proteoglycans are found in a variety of tissues, intracellular glandular secretions, extracellular matrix, and cell surface. Due to the presence of sulfate in the glycosaminoglycan section, these compounds have a high negative charge; therefore, they interact with small cations, enzymes, growth factors, and a number of pathogens such as viruses[14]. Sulfate heparin is very effective in binding viral particles and is involved in many viral infections; therefore, by inhibiting the virus binding to these compounds, the rate of viral infections, especially AIDS virus, can be reduced[15]. One hypothesis for the performance of antiviral peptides is that these compounds interact with heparin sulfate due to their positive charge and are effective in treating infections by preventing the binding of viral particles. It has been shown that alpha human diphenesin LL-37 and Magainin interact with molecules of different glucosamine aminoglycans. Human and cow's Lactoferricin also can interact with these compounds and can have antiviral effects. Research shows that Lactoferrin and a group of peptides with a short alpha structure can inhibit smallpox virus infections by binding to cell surface sulfate heparin[16&17].

Another mechanism used by peptides to inhibit viral effects is to prevent the virus from spreading from one cell to another. Such peptides include NP-1. NP-1 prevents Herpes simplex (HSV) viral infections[18].

On the other hand, the peptide interacts with the surface-covering glycoproteins of the virus and disrupts the function of the virus-covering glycoproteins. Covering glycoproteins are involved in the entry of the virus into the host cell. For example, retrocyclin-1 peptide binds to glycoproteins at the level of the Acquired immunodeficiency syndrome (AIDS) virus and has a major effect on inhibiting the virus's function. K-Difensins benefit greatly from this mechanism. These compounds prevent the virus from merging with the host cell by binding to the virus cover[19]. Some peptides can damage viral envelope and influences the attachment, the entry of the virus into the host cell as well as the following post infection phase. Other mechanisms, such as intracellular targets and the effect on infected cells and the progression of cell death, have also been suggested for antiviral peptides[20]. Due to similar mechanism for COVID-19 for cellular infection, antimicrobial peptide can reduce the infection of this virus by any mentioned mechanisms[21&22].

COVID-19 and AMPs

It's proven that antimalarial drugs can efficiently inhibit COVID-19. Treatment of COVID-19 by hydroxychloroquine (HCQ), a derivative of chloroquine, has considered as potent treatment of COVID-19 to some extent. Chloroquine and HCQ have been used for treating malaria[23]. Different studies suggested Combination therapy with hydroxychloroquine and antibiotic azithromycin for COVID-19. The U.S. Food and Drug Administration has authorized emergency use of both chloroquine and HCQ for COVID-19 patients. HCQ can efficiently inhibit SARS-CoV-2 infection with its anti-inflammatory function and good potential to combat the disease[24]. Thirty-three AMPs have been discovered from different sources[25]. As mentioned above, Combination therapy with hydroxychloroquine and antibiotic was used for treatment of COVID-19[26]. These 33 peptides have both antimicrobial and antiviral activities as well as anti-inflammatory function[25]. So, it is possible that these peptides, similar to antimalarial drugs and antibiotics, may be effective in reducing COVID-19 infection.

COVID-19 and antiviral peptides

Due to similarity of SARS-CoV-2 with other viruses, antiviral peptides can inhibit COVID-19 by above mentioned mechanisms. Antiviral peptides can inhibit COVID-19 by direct inhibiting SARS-CoV-2 particle. This inhibition can occur indirectly by attachment of peptide to viral link site on the host cell membrane and preventing the viral interaction

and adsorption with host cells. Other stages of SARS-CoV-2 cycle can also suppress by antiviral activity for example viral penetration, viral gene expression, and mature virions. For example, mucroporin-M1 is a scorpion venom-derived synthetic peptide with antiviral activity against SARS-CoV virus with direct interaction with virus envelope[27]. On the other hand, antimicrobial peptides cane enhance the host immunity against viral infection[28]. Based on literature review, AMPs have antiviral activity against enveloped RNA and DNA viruses[29]. However, these peptides have no inhibitory effects on some nonenveloped viruses[30]. There are two defined mechanisms for antiviral activity of AMPs: direct effect on the viral envelope and indirect effect on molecular process[31]. The most of AMPs have positive charge due to presence of Lysine and Arginine. This positive charge lead to electrostatic interaction with negatively charged cell surface molecules such as heparan sulfate. This compound has a key role in viral attachment and infection. Electrostatic interaction between AMPs and negative compound such as heparan sulfate can reduce viral attachment and infection[32]. The previous studies showed that AMPs have potent antiviral activity against similar viruses to SARS-CoV-2 such as Human Immunodeficiency Virus (HIV), influenza A viruses, vesicular stomatitis virus (VSV), Ebola virus, and etc. So, AMPs are also suitable compounds for drug design against SARS-CoV-2[33&34].

On the other hand, it's possible to design new synthetic antiviral peptides based on the structure of the existing peptides and properties of SARS-CoV-2. SARS-CoV-2 has positive-sense RNA. This virus, similar to other viral particles, is composed by spike glycoprotein, the envelope, the membrane, and the nucleocapsid. In all coronaviruses, the spike has two subunits: S1 and S2. This spike has important role in viral fusion process. Entrance of virus to host cell is related to this spike and its subunits. S2 subunit has fusion peptide (FP) and two heptads repeat regions (HR-N and HR-C)[35]. These subunits are suitable targets for vaccine design. Disruption of structures of spike leads to inhibition of viral fusion and prevention of infection. In similar studies, synthetic antiviral peptides were designed for inhibition of Middle East respiratory syndrome coronavirus (MERS-CoV). This synthetic peptide had potent inhibitory activity against MERS-CoV. This peptide designed based on properties of HR2 and the HR1 regions of MERS-CoV. These peptides can interact with viral HR1 domain and inhibit the formation of viral fusion core. MERS-5HB, 229E-HR1P, and 229E-HR2P are another synthetic antiviral peptide that contain three copies of HR1 and two copies of HR2. These peptides can inhibit both the MERS virus[36&37]. Similar peptide design can be used for S1 and S2 in SARS-CoV-2. The role of S1 and S2 is attachment of virus to host angiotensin-converting enzyme 2 (ACE2) receptor and attachment of virus to host cell membrane, respectively. The S1 has two domains: N-terminal domain (NTD) and three C-terminal domains (CTDs) with receptor-binding domain (RBD) for binding with hACE2 receptor[38]. Amino acid contents of RBD is: Tyr, Asn, Gly, Thr, Leu, Phe, and Gln. Heptad repeats (HR), transmembrane domain (TM), internal membrane fusion peptide (FP), and membrane-proximal external region (MPER) are located in S2 subunit[39]. Due to stability of HRs and their role in membrane fusion process, they are the best fusion inhibitors targeting[40]. SBP1, a 23-mer peptide (IEEQAKTFLDKFNHEAEDLFYQS), can use as SARS-CoV-2 spike protein binder and inhibit viral attachment[41&42]. Xia *et al.* developed series of lipopeptides derived from EK1 with ability to inhibition of SARS-CoV-2 S protein-mediated membrane fusion. These peptides showed antiviral activity against CoVs, MERS-CoV, and SARS-CoV-2[43]. Karoyan *et al.* designed hACE2 mimics peptides. These designed peptides can block SARS-CoV-2 human pulmonary cell infection. Surprisingly, these mimics' peptides can inhibit viral growth with IC50 in very low concentrations (Nano molar)[44]. Mucroporin-derivated peptide, Mucroporin-M1, showed antiviral activity against influenza H5N1, pseudoviruses, and SARS-CoV. This peptide interact and disrupt the viral envelope by electrostatic interaction[45]. Zhao *et al.* designed a new peptide based on β-defensins-4 that bind to the S2 subunit of MERS-CoV. This binding lead to inhibition of viral entry into the host cell. HD5 peptide with ability to binding to glycosylated proteins and lipid components, can inhibit S protein of SARS-CoV-2 and

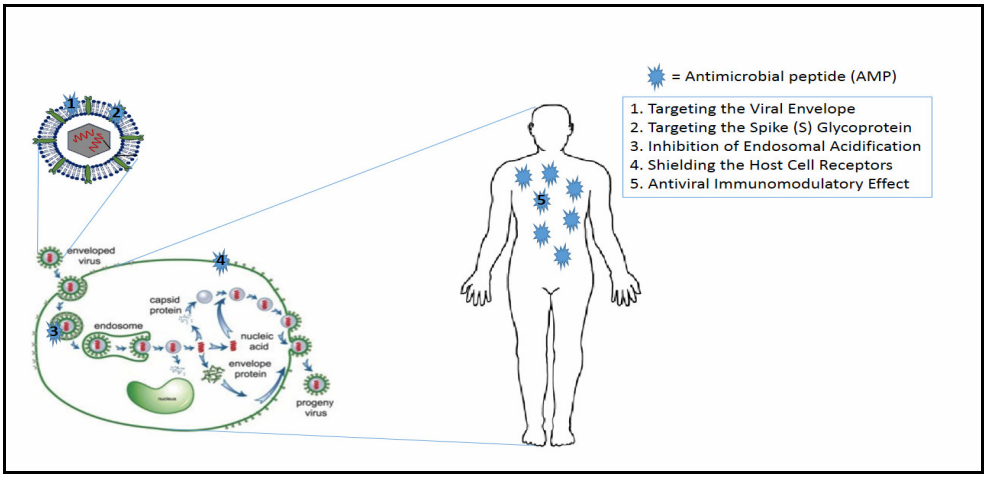

Fig. 2: Schematic of different strategies for inhibition of viral growth by peptides.

ACE2[46]. Wohlford-Lenane *et al.* showed that RTD-1 peptide can act as immunomodulatory effector molecule. This peptide induce proinflammatory cytokine response for elimination of SARS-CoV[47]. Based on this literature review and similarity of SARS-CoV-2 and other related viruses, there are five strategies for inhibition of viral growth by peptides. These mechanism was also shown in schematic figure 2.

Conclusion

Due to no available treatment for COVID-19, the pandemic of this virus has real threats for worldwide population. So, new antiviral agents for treatment and improvement of COVID-19 disease are indispensable. Antiviral peptides are considered as potent therapeutic drugs for control of viral infection, such as COVID-19. However, there are some limitations for antiviral peptides application such as high cost, short half-life, and correct delivery systems. These limitations can be solved by improving synthesis and purification systems such as recombinant peptide expression, post-translational modifications such as amidation and acetylation for improvement of stability, and use drug delivery systems such as nanostructures for targeted delivery.

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[٨]مركز أبحاث العلاج الخلوي للأطفال ، جامعة طهران للعلوم الطبية ، طهران ، إيران

[٩]قسم الطب الباطني ، جامعة شهيد سادوقى للعلوم الطبية ، يزد ، ايران

[١٠]مركز بحوث السياسة الصحية والإدارة ، كلية الصحة العامة ، جامعة شهيد سادوقي للعلوم الطبية ، يزد ، إيران

[١١]قسم الوراثة ، كلية الطب ، جامعة شهيد صدوقي للعلوم الطبية ، يزد ، إيران

[١٢]قسم غرفة العمليات والتخدير ، كلية العلوم الطبية المساعدة ، إيران

[١٣]قسم الأحياء ، كلية العلوم ، جامعة العلوم والفنون ، إيران

[١٤]مستشفى شهيد سادوقي ، جامعة شهيد سادوقي للعلوم الطبية ، يزد ، إيران

كوفيد-١٩هو مرض معد يسببه فيروس كورونا مستجد تم تحديده في الصين ، SARS-COV2.
لا توجد حتى الآن علاجات فعالة لـ كوفيد-١٩. لذلك ، من الضروري البحث عن علاجات جديدة لهذه المشكلة.

بسبب آلية محددة لتثبيط نمو الميكروبات ، يمكن اعتبار البيتيدات المضادة للميكروبات كأحد أفضل العلاجات في هذا المجال. البيتيدات المضادة للميكروبات (AMPs) هي عوامل مهمة يصنعها الجهاز المناعي استجابة لمسببات الأمراض. هذا النوع من الاستجابة المناعية موجود في جميع فئات

الحيوانات من بدائيات النوى إلى البشر. تم تحديد أنواع مختلفة من AMPs وعزلها من كائنات مختلفة من البكتيريا إلى البشر. حتى الآن ، تم استخراج ١٩٠ من الببتيدات المضادة للفيروسات ذات التأثيرات المضادة للفيروسات من مصادر حيوانية مختلفة. هذه المركبات الطبيعية ومشتقاتها، على سبيل المثال الببتيدات الاصطناعية ، يمكن اعتبارها أهدافًا علاجية جديدة في كوفيد-١٩. في هذا البحث المرجعى ، قمنا بتقييم هذه الببتيدات في فئات حيوانية مختلفة وكذلك الببتيدات الاصطناعية وإمكانية استخدام هذه المركبات في علاج كوفيد-١٩.