

## POTENTIAL ANIMAL SOURCES FOR DEVELOPMENT OF ANTIVIRAL THERAPEUTICS

### ABSTRACT

In line with the researches, due to the serious effects of viral infections on humans, anti-viral compound research has gained momentum and has become very important. In particular, viruses such as Cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis B and C viruses (HBV and HCV, respectively), herpes simplex virus (HSV), human immunodeficiency virus (HIV), rabies virus and Ebola virus are of high importance. Very few antiviral drugs commercially available can cause serious and significant side effects for patients receiving treatment. Also, viruses have the mutational capacity to infect host cells. For this reason, in recent years, the possibility of producing new antiviral drugs, especially from natural products, has increased considerably, and animal-based products have started to be used among natural product sources. Viral-borne infections have been known since ancient times. However, it was only possible to isolate these viruses that cause infection in the nineteenth century. The control of viral infection, the isolation of the virus, and the control of viral reproduction have played a role in the development of many drugs and vaccines in the studies carried out since that period. In addition to these studies, viruses continue to be one of the main causes of human and animal diseases today. It has been stated that Antiviral Peptides (AVPs) can be used as a defense barrier with previous studies. Some AVPs are known to show a broad spectrum against viruses. In this direction, many studies have been conducted on AVPs and it has been observed that these peptides inhibit the viral particle by the above-mentioned mechanisms.

**Keywords:** Animal sources, antiviral compounds, SARS-CoV-2, natural therapeutics.

### INTRODUCTION

In line with the researches, due to the serious effects of viral infections on humans, anti-viral compound research has gained momentum and become very important. In particular, viruses such as Cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis B and C viruses (HBV and HCV, respectively), herpes simplex virus (HSV), human immunodeficiency virus (HIV), rabies virus and Ebola virus are of high importance. Very few antiviral drugs commercially available can cause serious and significant side effects for patients receiving treatment. Also, viruses have the mutational capacity to infect host cells. For this reason, in recent years, the possibility of producing new antiviral drugs, especially from natural products, has increased considerably, and animal-based products have started to be used among natural product sources. Despite the detrimental mechanism of action of animal venoms, many are known to have potential medicinal properties to cure diseases. It is known that animal poisons are rich sources of antimicrobial agents and contain a wide variety of active biological compounds with different chemical structures. Antimicrobial peptides (AMPs), a group of peptides produced against pathogenic organisms such as bacteria, fungi, and viruses are considered the first line of defense for many organisms. These peptides show anti-viral activity by preventing virus particles from binding to the cell membrane surface, interfering with virus replication, preventing viral DNA from leaving the capsid or being transported to the nucleus. Because of its neurotoxic effect of biologically active peptides contained in scorpion venoms, its activity against retroviruses such as HIV / SIV has been proven. By rupturing the viral envelope

directly, AMPs in scorpion venom reduce viral infectivity and can inhibit or block the virion from entering the cell by occupying host cell receptors used by viral glycoproteins. Snake venoms and their components have been reported to show antiviral activity against measles virus, Sendai virus, dengue virus (DENV), yellow fever virus (YFV) and HIV. Therefore, snake venoms are sources of promising candidates for new antiviral drugs. Snake venoms are exhibiting anti-viral activity by interacting with host cells, preventing intracellular release of the virus capsid protein and blocking viral entry. In insects, *Vespula lewisii* demonstrates a broad spectrum of anti-viral activity against enveloped viruses by impairing pore formation by penetration of the viral lipidic envelope. *Apis mellifera* venom was found to exhibit virucidal activity against HIV-1. It has been observed that anti-viral cationic peptides obtained from marine organisms interact with the viral envelope of HSV types 1 and 2 and inhibit the infection of sensitive cells [1-5].

### **Animal Originated Antiviral Compounds**

Viral-borne infections have been known since the ancient times. However, it was only possible to isolate these viruses that cause infection in the nineteenth century. The control of viral infection, the isolation of the virus, and the control of viral reproduction have played a role in the development of many drugs and vaccines in the studies carried out since that period. Despite these studies, viruses continue to be one of the main causes of human and animal diseases today. The reason for this is that vaccine and drug development for viral infections are very difficult. For this reason, studies on the use of alternative antiviral substances have gained momentum. In general, the mechanism of action of antiviral drugs can exert an antiviral effect through inhibition of proteases, polymerases, and replication enzymes. However, the inadequacy of studies on researching antiviral mechanisms negatively affects the development of drugs and vaccines. Therefore, an attempt is made to research and develop alternative antiviral substances. [5-13].

Examining the studies conducted for the development of antiviral agents in the past, it was determined that antivirals may cause serious side effects in patients due to their weak specificity. One example of antiviral agents that act by inhibiting replication is the substance vidarabine. This substance inhibits viral DNA with polymerase enzymes. However, it affects the host cell negatively and causes serious side effects. In line with this premise, the tendency towards antiviral agents with less side effects has increased. However, limitations due to side effects of these agents decreased their effectiveness towards viral infections. For example, acyclovir antiviral agent causes low side effects in patients. However, due to its low effectiveness, it was insufficient in eliminating the infection. In addition, due to the low effect of the antiviral agent, viral resistance may develop and cause further infection. Therefore, with the increasing preference for molecules capable of broad-spectrum activity, the demand for the production of new antiviral drugs is higher than ever [5-13].

Some peptides of animal origin can show virucidal activity. Generally, these peptides are known to exert antiviral effects by preventing virus particles from binding to the cell membrane or by interfering with virus replication. Due to the limited use of antiviral drugs and their insufficient efficacy, the potential of antiviral peptides to be used as therapeutic agents has gained importance. The high side effects of synthetically developed drugs have increased the research of animal antiviral substances. The most basic criterion is that a compound to be used as an antiviral is being compatible with the infection cycle of the virus. The effect of the potential antiviral molecule is to inhibit the binding of the virus to the host cell in the first step. Thus, the antiviral candidate should prevent the virus from binding to the membrane and inhibit the onset of infection at the most basic point. Besides, antiviral candidates play an important role in preventing virus DNA or RNA from leaving the capsid

and entering the host cell. This antiviral effect is one of the functional activities that prevent the development of infection. Apart from these; there are also antiviral effects such as blocking viral reverse transcriptase activity, preventing viral DNA from being transported to the nucleus, and preventing the integration of viral DNA into the cellular chromosome. Because of these effects, studies on the use of animal-derived antivirals have gained momentum. In line with these studies, the importance of antiviral peptides (AVPs) of animal origin with a wide antiviral spectrum has increased. AVP molecules can generally exert an antiviral effect by directly inhibiting the viral particle, inhibiting the protein binding site in the host cell membrane and interfering with adsorption [5-13].

### **Animal Antiviral Peptides**

It has been stated that AVPs can be used as a defense barrier with previous studies. Some AVPs are known to show a broad spectrum against viruses. In this direction, many studies have been conducted on AVPs and it has been observed that these peptides inhibit the viral particles by the above-mentioned mechanisms. Details of AVPs obtained from animals are given below [14,15].

### **Antiviral peptides derived from scorpions**

The poisons used by arachnids for hunting and feeding have a rich molecular variety. These poisons have a deadly effect on humans. However, drug development studies from compounds obtained from these poisons have increased. Identified scorpion venoms are at an important point in medicinal potential drug development. Disulfide-bridged peptides and non-disulfide-bridged peptides found biologically in scorpions appear as neurotoxic poisons. These AVPs are an important drug source for the treatment of various diseases, especially diseases affecting the nervous system. It is also an important resource for the use of these poisons in antiviral drugs. Regarding the activity of scorpion venom compounds, it has been stated to be effective against many viruses. In particular, it has been determined that the peptide named Smp76 isolated from the *Scorpio maurus palmatus* venom has antiviral effects against many type of viruses. The scorpion species from which these poisons are obtained and the virus groups where they are effective are indicated in Table 1 [5,10,16,17].

### **Antiviral peptides derived from snakes**

The rich composition of snake venom is at the top of the drug sources for new drugs to be developed. It contains proteins, peptides, free amino acids and metallic elements. It contains particularly effective ingredients to provide antimicrobial effect. Studies have proven that snake venoms are effective on many microorganisms by hydrolyzing phospholipids. In this way, studies for snake venoms, whose antibacterial effect has been determined, may focus on their antiviral properties. Some studies have reported antiviral activity of snake venoms and their components against measles virus, Sendai virus, dengue virus (DENV), yellow fever virus and HIV. It has been reported that snake venom used as supplementary treatment in viral infections. Snake venom seems to be one of the most important antiviral sources when considering the possibility of HIV-1 virus binding to the same receptor due to its long neurotoxin cycle. The catalytic effect of snake venom by means of enzymes, the cell-binding effect and the induction effect at the membrane level are important issues. The snake species from which these poisons are obtained and the virus groups where they are effective are indicated in Table 1 [5,10,18].

### **Antiviral peptides derived from insects**

Insects are amongst the classes of animals resistant to bacterial and viral infections. Insects have an effective naturally developed defense system. In addition to the innate immune

system, mammals also have an acquired immune system. However, thanks to the peptides they develop with the innate immune system, insects can produce proteins with antimicrobial and antiviral effects. In this way, insects have a system to quickly remove the pathogen. The reason for the antimicrobial effect developed in insects is the development of rapidly developing antimicrobial peptides (AMP) and AVPs. Mastoparan, cecropins, melittin and allogenins developed by insects are the main proteins that create antimicrobial and antiviral effect. In studies conducted, mastoparan peptides have shown a broad spectrum of antiviral activity against enveloped viruses such as *Rhabdoviridae*, *Poxviridae*, *Flaviridae*, *Paramyxoviridae* and *Herpesviridae*. The antiviral effect of cecropins, melittin and allogenin peptides against virus groups such as influenza virus, HIV-1 has been proven. There are antiviral activities defined for melittin obtained from bees and wasps. It is known that melittin and its derivatives obtained from these creatures are effective on the herpes virus. Melittin is an important resource for antiviral drugs that will be developed to have an antiviral effect especially on the herpes virus. The insect species from which these AVPs are obtained and the virus groups where they are effective are indicated in Table 1 [5,10,19,20,21].

### Antiviral peptides derived from aquatic organisms

Aquatic organisms are also promising sources of antiviral cationic peptides. Many different peptides in their structure can show activity against viruses and other pathogens. It is also known that the skin secretions of amphibians have strong antiviral effects. Such skin secretions constitute the primary immune system of amphibians. The antimicrobial, antineoplastic, antiviral activity of secretions produced by the skin granular glands of amphibians is known. Pharmaceutical products synthesized from these antimicrobial peptides are known to exhibit cytotoxic effects and anti-herpetic activity. For example, magainin 1 and 2 isolated from *Xenopus laevis* frog tested against HSV-1 and -2 and showed effective inhibition of both viruses. Peptides were effective by disrupting the viral envelope. There are also studies on the antiviral activity of some peptides isolated from tunicates, sponges and fish. [5,10].

**Table 1.** Animal antiviral peptides and their therapeutic effect [5-21].

Animal Type	Compound Type	Virus Effective	Therapeutic Effect
<i>Bothrops jararaca</i>	Venom	DENV-3	Reducing infected cells
<i>Crotalus durissus terrificus</i>	Venom	DENV, YFV, HCV	Virus envelope cleavage and protein imbalance
<i>Bothrops leucurus</i>	Venom	DENV	Reducing the viral RNA level
<i>Naja kaouthia (Naja siamensis)</i>	Venom	HIV	Protein inhibition
<i>Tachypleus tridentatus</i>	Toxin	HIV	Viral receptor effect
<i>Trididemnum solidum</i>	Toxin	HSV-1, HSV-2	Protein, DNA and RNA synthesis inhibition
<i>Vespula lewisii</i>	Venom	VSV, HSV-1, YFV, RSV,	Viral envelope disruption

		WNV	
<i>Homophymia sp.</i>	Toxin	HIV	Inhibition of virion penetration
<i>Theonella sp.</i>	Toxin	HIV	Inhibition of virion penetration
<i>Theonella swinhoe</i>	Toxin	HIV	Inhibition of virion penetration
<i>T. swinhoe ve T. cupola</i>	Toxin	HIV	Inhibition of virion penetration
<i>Siliquariaspongia mirabilis</i>	Toxin	HIV	Inhibition of virion penetration
<i>Callipelta sp.</i>	Toxin	HIV	Inhibition of virion penetration
<i>Litoria chloris</i>	Toxin	HIV	Viral envelope disruption
<i>Mesobuthus martensii</i>	Venom	HIV-1	Viral envelope disruption
<i>Calliphora vicina</i>	Venom	IAV/HSV	Immunomodulatory activity
<i>Apis mellifera</i>	Toxin	HIV-1, HSV-1 and 2, Junin virus	Protein inhibition and inhibition of virion penetration
<i>Hyalophora cecropia</i>	Toxin	HIV, HSV-1 and 2, Junin virus	Virion entry blocking into host cell
<i>Litoria genimaculata</i>	Toxin	HIV	Viral envelope disruption
<i>Rana brevipodaporsa</i>	Toxin	HSV	Viral inactivation
<i>Phyllomedusa sp.</i>	Toxin	HSV-1, HSV-2, HIV, rabies virus	Viral envelope disruption
<i>Litoria caerulea</i>	Toxin	HIV	Viral envelope disruption
<i>Xenopus laevis</i>	Toxin	HSV-1, HSV-2	Cellular target
<i>Chaerilus tryznai</i>	Venom	HCV	Viral envelope disruption
<i>Heterometrus petersii</i>	Venom	HCV, HSV-1,	Viral envelope disruption
<i>Lychas mucronatus</i>	Venom	MeV, SARS-CoV, H5N1, HBV, HIV-1	Viral envelope disruption
<i>Pleuronectes americanus</i>	Toxin	HSV	Viral envelope disruption
<i>Trimeresurus stejnegeri</i>	Venom	HIV-1	Syncytium formation, antigen reduction

<i>Sidonops microspinosa</i>	Toxin	HIV	Cytopathic inhibition effect
<i>Neamphius huxleyi</i>	Toxin	HIV	Virion entry inhibition
<i>Naja nigricollis</i>	Venom	Sendai virus	Virus envelope cleavage and protein imbalance
<i>Bungarus candidus</i>	Venom	HIV	Viral inactivation
<i>Naja naja</i>	Venom	HIV	Viral inactivation
<i>Lachesana tarabaeve</i>	Venom	DENV-2	Viral inactivation
<i>Rana temporaria</i>	Toxin	HSV-1	Viral inactivation
<i>Styela clava</i>	Toxin	rotavirus; adenovirus, HSV, HIV	Viral inactivation
<i>Pleunorectus americanus</i>	Toxin	HSV-1; HSV-2	Viral inactivation

## CONCLUSION

It is noteworthy that animal sources should also be taken into account in the ongoing pharmaceutical product development studies for the SARS-CoV2 pandemic, further studies on the effectiveness of potent antiviral bioactive compounds in their composition against SARS-CoV2 and their stability towards the drug form development phase, considering that the use of natural derived resources as cost-effective and especially inhibitory reparations to prevent the spread of infections will become widespread from time to time, it is thought that it will be beneficial to increase the studies in this field.

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