



REVIEW ARTICLE

POTENTIAL ANIMAL POISONS FOR DEVELOPMENT OF ANTIVIRAL THERAPEUTICS

Gökhan CENGİZ¹ , Aslı ŞAHİNER² , Evren ALGIN YAPAR^{1*} , Bilge Ahsen KARA³ ,
 Rakesh K. SINDHU⁴

¹Ministry of Health, Turkish Medicines and Medical Devices Agency, Department of Analysis and Control Laboratories, Ankara, Turkey. ²Ege University, Faculty of Science, Department of Biology, Izmir, Turkey. ³Ministry of Health, Ankara Gazi Mustafa Kemal State Hospital, Ankara, Turkey. ⁴Chitkara College of Pharmacy, Chitkara University, Punjab, India.

Article Info:



Article History:

Received: 2 February 2021
 Reviewed: 7 March 2021
 Accepted: 10 April 2021
 Published: 15 May 2021

Cite this article:

CENGİZ G, ŞAHİNER A, ALGIN YAPAR E, KARA BA, SINDHU RK. Potential animal poisons for development of antiviral therapeutics. Universal Journal of Pharmaceutical Research 2021; 6(2):50-54. <https://doi.org/10.22270/ujpr.v6i2.564>

*Address for Correspondence:

Dr. George Zhu, University Hospital Leiden, The Netherlands.
 E-mail: sansan4240732@163.com

Abstract

Recent 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/HBV, Hepatitis C/HCV, Herpes Simplex Virus/HSV, Human Immunodeficiency Virus/HIV, rabies virus, corona virus and Ebola virus are of high importance. Very limited antiviral medicines commercially available and can cause serious-significant side effects for patients receiving treatment. Also, viruses have the mutational capability to infect host cells. For this reason, in recent years, the possibility of producing new antiviral medicines, especially from natural sources, has increased considerably, and animal-based products are now also promising among natural products. Viral-borne infections have been known long ago. However, it was just possible to isolate these viruses that cause infection in the nineteenth century. The management of viral infection, the isolation of the virus, and the control of viral reproduction has 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 primary 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. In this study venoms and toxins of some animals, which have antiviral activities are overviewed.

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

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 importance¹. Very limited antiviral medicines commercially available and can cause serious-significant side effects for patients receiving treatment. Also, viruses have the mutational capability to infect host cells. For this reason, in recent years, the possibility of producing new antiviral medicines,

especially from natural sources, has increased considerably, and animal-based products have started gaining recognition in terms of use among natural sources. Despite the detrimental mechanism of action of animal venoms, many are known to have medicinal potential to cure diseases. Animal poisons are known that they contain a broad range of active biological compounds have antimicrobial activity². These antimicrobial peptides (AMPs) are produced against pathogenic organisms such as fungus, bacteria and viruses, which are displaying the first line of defense for various microorganisms. They show anti-viral activity by preventing virus particles from binding to the cellular membrane surface, accomplishing by virus replication, preventing viral DNA from leaving the capsid or being transported to the nucleus³. The

efficacy on the retroviruses such as HIV/SIV of biologically active peptides including neurotoxic scorpion venoms has been proven by various research. By rupturing the viral envelope directly, AMPs in scorpion venom reduce viral infectivity and can inhibit or hinder the virion to enter the cell by invading the host receptors by using 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. In this context, snake venoms can be encouraging alternative sources for new antiviral medicines. Snake venoms are exhibiting anti-viral activity by interacting with host cell, blocking intracellular release of the virus capsid protein and hindering viral entering. In insects, *Vespula lewisii* demonstrates a wide spectrum of anti-viral efficacy to enveloped viruses by impairing pore formation by penetration of the viral lipidic envelope. *Apis mellifera* venom was found to exhibit virucidal activity against HIV-1⁴. It has been observed that anti-viral cationic peptides obtained from marine organisms interact to the viral envelope of HSV1 and HSV2 to prevent the infecting of sensitive cells⁵.

In this study it was aimed to overview venoms and toxins of some animals, which have antiviral activities and can be a potential source for new antiviral medicines.

Animal Originated Antiviral Compounds

Viral-borne infections have been existed long ago. However, the isolation of the viruses that cause infection had been achieved in the nineteenth century. The isolation of the virus, the control of viral reproduction and the treatment of viral diseases, have played a role in the development of many medicines and vaccines in the studies carried out since that period. Despite these studies, viruses continue to be important factor of human and animal diseases today. 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 substances⁵⁻¹³. 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 owing to their weak specificity. One of the antiviral agents that can be exemplified is the vidarabine acting by inhibiting replication. This substance inhibits viral DNA with polymerase enzymes. It also affects the host cell negatively and causes serious side effects. In line with this premise, the tendency towards antiviral agents with fewer side effects have 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. Additionally, due to its low effectiveness, it was

insufficient in eliminating the infection. Moreover, due to the low effect of the antiviral agent, viral resistance may develop and cause further infection. Therefore, with the increasing predilection for molecules with broad-spectrum activity, the requirement for the development of new generation antiviral medicines is higher than ever⁵⁻¹³. 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 cellular membrane or by interfering with virus replication. Due to the restricted use of antiviral medicines 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. Initially binding of the virus to the host cell is expected to inhibit by the candidate antiviral molecule, then 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 adsorption⁵⁻¹³.

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 development¹⁶. Disulfide-bridged peptides and non-disulfide-bridged peptides found biologically in scorpions appear as neurotoxic poisons. These AVPs are important medicinal sources for the cure of various infections, especially diseases affecting the nervous system. It is also an important resource for the use of these poisons in antiviral drugs¹⁷.

Table 1: Animal antiviral peptides and therapeutic effect⁵⁻²⁴.

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, WNV	Viral envelope disruption
<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 effect inhibition
<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>Pleurorectus americanus</i>	Toxin	HSV-1, HSV-2	Viral inactivation

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^{5,10,18,19}.

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 phospholipids²⁰. In this way, studies for snake venoms, whose antibacterial effect has been determined, may focus on their antiviral properties. It has reported in various studies that snake venoms and their components are affective on measles virus, Sendai virus, dengue virus, yellow fever virus and HIV. It has also 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 cycle⁵. 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^{5,10,21}.

Antiviral peptides derived from insects

Among the animals, the insects are known that 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 AMP and AVPs. Mastoparan, cecropins, melittin and alloferons developed by insects are the main proteins that create antimicrobial and antiviral effect. In studies mastoparan peptides broad spectrum of antiviral efficacy on the enveloped viruses such as *Rhabdoviridae*, *Poxviridae*, *Flaviridae*, *Paramyxoviridae* and *Herpesviridae* have been indicated and the antiviral effect of cecropins, melittin and alloferon peptides against virus groups such as influenza virus, HIV-1 have 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^{5,10,22,23,24}.

Antiviral peptides derived from aquatic organisms

Aquatic organisms, which are the potential sources of various antiviral cationic peptides, are other promising candidates for antiviral medicines development. Many different peptides in their structure can show antiviral activity on 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 various studies indicating the antiviral potential of some peptides isolated from tunicates, sponges and fish^{5,10}.

CONCLUSIONS

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.

ACKNOWLEDGEMENTS

The authors extend their thanks and appreciation to the Turkish Medicines and Medical Devices Agency, Department of Analysis and Control Laboratories, Ankara, Turkey to provide necessary facilities for this work.

AUTHOR'S CONTRIBUTION

ALGIN YAPAR E: writing original draft, literature survey. **CENGİZ G:** methodology, conceptualization. **ŞAHİNER A:** formal analysis, review. **KARA BA:** investigation, conceptualization. **SINDHU RK:** critical review. All authors revised the article and approved the final version.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

REFERENCES

1. Bordon KDCF, Bologna CT, Fornari-Baldo EC, *et al.* From animal poisons and venoms to medicines: achievements, challenges and perspectives in drug discovery. *Front Pharmacol* 2020; 11: 1132. <https://doi.org/10.3389/fphar.2020.01132>
2. Memariani H, Memariani M, Moravvej H, Shahidi-Dadras M. Melittin: a venom-derived peptide with promising antiviral properties. *Eur J Clin Microbiol Infect Dis* 2020; 39(1):5-17. <https://doi.org/10.1007/s10096-019-03674-0>
3. Yacoub T, Rima M, Karam M, Fajloun JSZ. Antimicrobials from Venomous Animals: An Overview. *Molecules* 2020; 25(10):2402. <https://doi.org/10.3390/molecules25102402>
4. Mohamed Abd El-Aziz, T, Soares AG, Stockand JD. Snake venoms in drug discovery: valuable therapeutic tools for life saving. *Toxins* 2019; 11(10): 564. <https://doi.org/10.3390/toxins11100564>
5. da Mata ÉCG, Mourão CBF, Rangel M, *et al.* Antiviral activity of animal venom peptides and related compounds. *J Venom Anim Toxins Incl Trop Dis* 2017; 23(3): 1-12. <https://doi.org/10.1186/s40409-016-0089-0>
6. Torres TS, Cardoso SW, Velasque LS, Veloso VG, Grinsztejn B. Incidence rate of modifying or discontinuing first combined antiretroviral therapy regimen due to toxicity during the first year of treatment stratified by age. *Braz J Infec Dis* 2014; 18(1):34-41. <https://doi.org/10.1016/j.bjid.2013.04.005>

7. Moreno M, Giralt E. Three valuable peptides from bee and wasp venoms for therapeutic and biotechnological use: Melittin, Apamin and Mastoparan. *Toxins (Basel)* 2015; 7: 1126-1150. <https://doi.org/10.3390/toxins7041126>
8. Baghian A, Jaynes J, Enright F, Kousoulas KG. An amphipathic alpha-helical synthetic peptide analogue of melittin inhibits herpes simplex virus-1 (HSV-1)-induced cell fusion and virus spread. *Peptides* 1997; 18: 177-183. [https://doi.org/10.1016/s0196-9781\(96\)00290-2](https://doi.org/10.1016/s0196-9781(96)00290-2)
9. Hood JL, Jallouk AP, Campbell N, Ratner L, Wickline SA. Cytolytic nanoparticles attenuate HIV-1 infectivity. *Antivir Ther* 2013; 18:95-103. <https://doi.org/10.3851/IMP2346>
10. Vilas Boas LCP, Campos ML, Berlanda RLA, Franco OL, Neves NC. Antiviral peptides as promising therapeutic drugs. *Cell Mol Life Sci* 2019; 76:3525-3542. <https://doi.org/10.1007/s00018-019-03138-w>
11. Galdiero S, Falanga A, Tarallo R, *et al.* Peptide inhibitors against herpes simplex virus infections. *J Pept Sci* 2013; 19:148-158. <https://doi.org/10.1002/psc.2489>
12. Bulet P, Stöcklin R, Menin L. Anti-microbial peptides: from invertebrates to vertebrates. *Immunol Rev* 2004;198:169-184. <https://doi.org/10.1111/j.0105-2896.2004.0124.x>
13. Badani H, Garry RF, Wimley WC. Peptide entry inhibitors of enveloped viruses: the importance of interfacial hydrophobicity. *Biochim Biophys Acta Biomembr* 2014; 1838:2180-2197. <https://doi.org/10.1016/j.bbmem.2014.04.015>
14. Slocinska M, Marciniak P, Rosinski G. Insects antiviral and anticancer peptides: new leads for the future? *Protein Pept Lett* 2008; 15(6): 578-585. <https://doi.org/10.2174/092986608784966912>
15. Florisa R, Recio I, Berkhout B, Visser S. Antibacterial and antiviral effects of milk proteins and derivatives thereof. *Curr Pharm Des* 2003; 9(16):1257-75. <https://doi.org/10.2174/1381612033454810>
16. Zhang Y. Why do we study animal toxins? *Dongwuxue Yanjiu* 2015; 36(4):183-222. <https://doi.org/10.13918/j.issn.2095-8137.2015.4.183>
17. Almaaytah A, Albalas Q. Scorpion venom peptides with no disulfide bridges: a review. *Peptides* 2014; 51:35-45. <https://doi.org/10.1016/j.peptides.2013.10.021>
18. Li Q, Zhao Z, Zhou D, Chen Y, *et al.* Virucidal activity of a scorpion venom peptide variant mucroporin-M1 against measles, SARS-CoV and influenza H5N1 viruses. *Peptides* 2011; 32(7):1518-25. <https://doi.org/10.1016/j.peptides.2011.05.015>
19. El-Bitar AM, Sarhan MM, Aoki C, *et al.* Virocidal activity of Egyptian scorpion venoms against hepatitis C virus Hepatitis viruses. *Virology* 2015; 24(12):1-9. <https://doi.org/10.1186/s12985-015-0276-6>
20. Mohamed Abd El-Aziz T, Garcia Soares A, Stockand JD. Snake venoms in drug discovery: Valuable therapeutic tools for life saving. *Toxins (Basel)* 2019; 11(10): 564. <https://doi.org/10.3390/toxins11100564>
21. Shimizu JF, Pereira CM, Bittar C, *et al.* Multiple effects of toxins isolated from *Crotalus durissus terrificus* on the hepatitis C virus life cycle. *PLoS One* 2017; 12(11): e0187857. <https://doi.org/10.1371/journal.pone.0187857>
22. Hood JL, Jallouk AP, Campbell N, Ratner L, Wickline SA. Cytolytic nanoparticles attenuate HIV-1 infectivity. *Antivir Ther* 2013;18(1):95-103. <https://doi.org/10.3851/IMP2346>
23. Chernysh S, Kim SI, Bekker G, *et al.* Antiviral and antitumor peptides from insects. *Proc Natl Acad Sci USA* 2002; 99:12628-12632. <https://doi.org/10.1073/pnas.192301899>
24. Hultmark D, Steiner H, Rasmuson T, Boman HG. Insect immunity. Purification and properties of three inducible bactericidal proteins from hemolymph of immunized pupae of *Hyalophora cecropia*. *Eur J Biochem* 2005; 106:7-16. <https://doi.org/10.1111/j.1432-1033.1980.tb05991.x>