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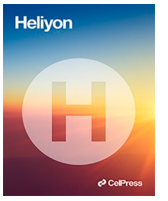

Review article

An in-depth exploration of snake venom-derived molecules for drug discovery in advancing antiviral therapeutics

Hicham Hboub [a], Reda Ben Mrid [a], Najat Bouchmaa [a], Naoual Oukkache [b], Rachid El Fatimy [a,*]

[a] *Institute of Biological Sciences (ISSB), Faculty of Medical Sciences (FMS), Mohammed VI Polytechnic University (UM6P), Ben Guerir, 43150, Morocco*

[b] *Laboratory of Venoms and Toxins, Pasteur Institute of Morocco, Casablanca, 20360, Morocco*

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ABSTRACT

Snake venom is a cocktail and rich source of various bioactive compounds that have been extensively studied for their potential as pharmaceutical agents due to their diverse chemical structures and wide range of biological activities. In light of the emergency and the re-emergence of viral infectious diseases that threaten human health and economic systems, exploring new fertile and rich fields such as snake venom is an attractive path for anti-viral drug discovery, especially in the lack of effective vaccines. Although 85 % of reported antiviral molecules belong to the phospholipase A2 (PLA2) family, other protein families including L-amino acid oxidases (LAAO), disintegrins, metalloproteases (SVMPs), and cathelicidins have also shown antiviral activity. Thus, in this review, we have highlighted the antiviral properties of compounds derived from snake venom and their mechanisms of action against virus classes like HIV, *Coronaviridae*, *Flaviviridae*, and *Paramyxoviridae*. Although the initial research emphasis has been on *Retroviridae* (HIV) and *Flaviviridae* viruses, it is crucial to extend the exploration of the potential of these compounds to other viruses. The utilization of snake venom-derived compounds as antivirals shows significant promise for the development of novel therapeutics to address viral infections. However, a more in-depth investigation is necessary to fully assess the potential of these compounds against other viruses and unveil the mechanisms underlying their action.

1. Introduction

Venom is a complex cocktail of components that are secreted by venom glands – as in the case of snakes - or stored in different tissues or cells of venomous animals [1], This latter represents approximately 15 % of all described animal species, and can belong to vertebrates (e.g., snakes) or invertebrates (e.g., spiders, scorpions, jellyfish, and others) [1,2]. Venomous animals are part of various phyla including Chordata (e.g., snakes), Cnidaria (e.g., jellyfish), Echinodermata (e.g., starfishes), Mollusca (e.g., snails), Arthropods (e.g., scorpions), and Annelida (e.g. leech) [3]. Moreover, venomous snakes are of particular medical significance due to the danger of snakebites to human beings [4]. Regarding their clinical impact, venoms are classified into neurotoxins, myotoxins, hemotoxins, cardiotoxins, anti-coagulants, procoagulants, necrotoxins, nephrotoxins, and other toxins [4]. Venomics is a field of research that involves the use of advanced and high-throughput technologies to investigate the composition of venoms through proteomic,

* Corresponding author.
E-mail address: rachid.elfatimy@um6p.ma (R. El Fatimy).

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transcriptomic, and genomic studies [5]. Hence, the state–of–the–art technologies – in this area – are the principal actors that enhanced the discovery of the enormous diversity of venoms and the characterization of their composition and identification of their molecules [5]. In this context, snake venom is the most extensively studied and characterized animal venom due to the large amount of venom that can be extracted from each snake compared to other small venomous animals [6,7]. In fact, the quantity of venom produced by snakes can reach up to 900 mg per milking, as seen in the case of the King Cobra [8]. This contrasts with the smaller amounts produced by other animals, for example, only 1.22 mg per milking in the case of *Tityus discrepans* [9].

Venom-based drugs are a relatively new area of research compared to other natural sources of drugs such as microorganisms, plants, and fungi. Although the mentioned fact and the very limited approved toxin-derived drugs (11 drugs) [10], the angiotensin-converting enzyme (ACE) inhibitor Lisinopril used to treat hypertension and heath failure was the most prescribed drug over the world in 2018 and still in top four in 2021 according to the ClinCalc DrugStats Database [11,12]. Snake venom is composed of more than 90 % of proteins and peptides with the remaining minority consisting of carbohydrates, metal ions, inorganic anions, and lipids [13]. A sum of sixty-three families has been identified in snake proteins, although more than half (36 families) are classified as rare, and four families are the most abundant, including phospholipases A2 (PLA2), snake venom serine protease (SVSP), snake venom metalloprotease (SVMP) and three-finger toxin (3FTx) [14]. The first three families are proteins with enzymatic activities, while 3FTx are non-enzymatic proteins, which distinguishes them from the other families.

In addition, the snake venom appears to be an exception due to its unique composition and the abundance of available venom protein information, which enables greater flexibility in identifying and characterizing its components [5]. Snake venom exhibits a high variation among intraspecies and interspecies [15]. This rich diversity of snake venom compounds represents a potential repertoire to discover new drugs [15]. Consequently, researchers have directed greater attention towards snake venom compared to other venomous animals. The variation of the snake venom attributable to numerous factors such as the sex and age of snakes, environmental conditions, genetic factors, and the available preys [15,16]. In fact, a research study has shown the impact of particular shift in diet on venom toxicity (in terms of Lethal Dose 50) [17]. The researchers found that there is extensive variation in venom composition among *Echis* species groups. Particularly, venoms from the frequent arthropod-feeding *E. carinatus* and *E. ocellatus* groups were more toxic to arthropods than venoms from the mammal-feeding *E. pyramidum* and *E. coloratus* group [17]. By understanding and controlling the diet of snakes in a lab setting, researchers can manipulate venom composition to obtain desired toxicity profiles or enhance the production of specific venom components with potential therapeutic value. Additionally, this knowledge can guide researchers in exploring other venomous animals as potential sources of novel drug candidates and assist in developing more effective, targeted anti-venom treatments.

Viral infections are the group of diseases that occur due to viruses such as Human Immunodeficiency Virus (HIV), influenza virus, Nipah virus, hantavirus, Ebola virus, middle east respiratory syndrome (MERS) related coronavirus, and most recently, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). These viruses can affect different human systems, such as the respiratory, nervous, digestive, and endocrine systems, due to the intervention of different viruses like coronaviruses, enteroviruses, rotavirus, and HIV, respectively. Moreover, the emergency or the re-emergence of viral diseases is a significant global challenge to world health as these viruses can rapidly spread viruses and pose severe threats to the communities [18]. Currently, there are about 200 viruses with the ability to infect humans. Among them those listed in the world health organization (WHO)'s Disease Outbreak News (DON) that englobe infectious diseases with high priority, including influenza, MERS, and Ebola, listed in order of priority [19]. These infectious diseases require special attention due to their potential for a significant impact on public health.

Although vaccines are essential for curbing the spread of viral diseases and limiting their dangerousness, pharmaceuticals play a critical role in reducing mortality from these diseases, particularly in treating people who are already infected. Components of snake venom are of interest as new drugs for treating viral diseases, particularly in cases where effective treatments or vaccines are unavailable or inadequate for many viral infections. To date, numerous anti-viral components from snake venom have been identified with the most abundant protein family, Phospholipases A2 (PLA2), being particularly attractive for drug development [20].

Therefore, in this review, we've underscored a comprehensive and up-to-date repository of snake venom compounds from all protein families, focusing on their antiviral characteristics and mechanisms of action against virus families such as *Retroviridae*, *Coronaviridae*, *Flaviviridae*, and *Paramyxoviridae*. While the predominant research studies focus have initially centered on *Retroviridae* (HIV) and *Flaviviridae* viruses, it is imperative to broaden the investigation into the potential of these compounds against other emerging viruses. The extensive collection of compounds encompasses proteins, peptides, and crude venom derived from various families including PLA2, desintegrin, Metalloproteases, cathelicidins and L-Amino Acid Oxidase (LAAO). To facilitate a thorough understanding of their anti-viral properties, the review also explores the respective mechanisms of action for each compound.

2. Materials and Methods

We conducted a keyword-based search using terms such as "Snake Venom," "Venom," "Snake," "Virus," "Viral diseases," and "Antivirals." This search was performed across the Scopus, Google Scholar, and PubMed databases. Additionally, we meticulously reviewed relevant literature to ensure a thorough assessment of current studies in this area. Given the limited number of studies in this field, we did not restrict the search by publication dates, acknowledging that some significant compounds were discovered long ago. We applied minimal exclusion criteria, only omitting studies that were questionable (e.g., retracted articles) and in-silico studies, due to their rarity in snake venom research and lack of laboratory validation. The compound data compiled in Table 1 includes details on compound names and families, the originating snake family and species, the targeted virus families and species, and their antiviral properties. This information was utilized to create all the figures in the study.

Table 1
Snake venom-derived antiviral compounds and their antiviral properties.

Virus families	Virus species	Family	Name of active compounds	Source	Antiviral properties	R
Bunyaviridae	Oro-pouche virus	PLA2a	PLA2-CB	*Crotalus durissus terrificus*	Direct virucidal effect on virus particles	[92]
			crotoxin (CX)	*Crotalus durissus terrificus*		
Coronaviridae	BCoV	PLA2	HDP-1	*Naja haje haje*	virucidal activity: destruction of viral membrane	[65]
			HDP-2	*Naja haje haje*		
			Naja haje PLA2 (Nh-PLA2)	*Naja haje haje*	Virucidal activity: By interacting with the viral capsid, it may hinder the virus from attaching to host cells, thus inhibiting its spread.	[69]
	MERS-COV	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Low antiviral activity due probably to the size of spikes (PM budding site enhance activity instead of ERGIC)	[29]
	Sars-CoV-2	PLA2	HDP-1	*Vipera nikolskii*	Block SARS-CoV-2 glycoprotein S-mediated cell-cell fusion	[65]
			HDP-2		Inhibition of viral entry occurs by blocking SARS-CoV-2 spike glycoprotein-mediated cell-cell fusion and interaction with ACE2, as well as exhibiting virucidal activity (destruction of the viral membrane). Inhibition takes place during post-entry stages and continues throughout the entire process.	
			(p-BthTX-I)2 K	*Bothrops jararacussu*	Blocked the entry of the PLpro substrate.	[64]
					Resistant to plasma proteolysis, inhibits various SARS-CoV-2 strains, exhibits mild cytotoxic effects, and provides antithrombotic benefits.	[68]
Flaviviridae	DENV-1	PLA2	BlD-PLA2 (Asp49)	*Bothrops leucurus*	In addition to catalytic activity, the physiological role of BlPLA2s can be mediated by ligation to specific receptors on the cell membrane (interfering with the host cell components)	[93]
			BlK-PLA2 (Lys49)	*Bothrops leucurus*		
			Myotoxin-I (Mt-I)	*Bothrops asper*	Direct virucidal mechanism involving enzyme activity	[94]
			Myotoxin-II (Mt-II) PLA2 like	*Bothrops asper*	The same mechanism as Mt-I, although it exhibit weak antiviral effect (1000 times lower than Mt-I)	
	DENV-2	SBPM	Crotamine	*Crotalus durrissus terrificus*	Low selectivity compared to crotoxin, crotapotin and PLA2-CB	[95]
		PLA2	BthTX-I	*Bothrops jararacussu*	Antiviral activity in the virucidal, adsorption and internalization strategies	[96]
			Myotoxin-I (Mt-I)	*Bothrops asper*	Direct virucidal mechanism involving enzyme activity	[94]
			Myotoxin-II (Mt-II) PLA2 like	*Bothrops asper*	The same mechanism as Mt-I, although it exhibit weak antiviral effect (1000 times lower than Mt-I)	
			rPLA2-CB1	*Crotalus durissus terrificus*	Virucidal activity	[97]
			rPLA2-CB2	*Crotalus durissus terrificus*		
			Crotoxin	*Crotalus durissus terrificus*	Direct virucidal effect most provably by glycerophospholipid cleavage on the virus envelope, which would lead to disruption of the lipid bilayer and destabilization of the E proteins on the virus surface, with the consequence of inactivation	[92]
			PLA2-CB	*Crotalus durissus terrificus*		
			Crotoxin	*Crotalus durissus terrificus*	The highest inhibitions of viral replication were observed in the virucidal, pre-treatment and adsorption assays indicating that the inhibition	[96]

(*continued on next page*)

Table 1 (*continued*)

Virus families	Virus species	Family	Name of active compounds	Source	Antiviral properties	R
			PLA2-ICB	*Crotalus durissus terrificus*	occurs at the initial steps of the replication cycle	
			BlD-PLA2 (Asp49)	*Bothrops leucurus*	In addition to catalytic activity, the physiological role of BlPLA2s can be mediated by ligation to specific receptors on the cell membrane (interfering with the host cell components)	[93]
			BlK-PLA2 (Lys49)	*Bothrops leucurus*		
			CM-II-PLA2	*Naja mossambica mossambica*	direct virucidal mechanism	[29]
			Balt-PLA2	*Bothrops alternatus*	Direct virucidal effect (possible action of BaltPLA2 on DENV in the endoplasmic reticulum (ER), where assembly of the virus particles occurs, affecting the formation of the viral envelope and decreases the formation of new viral particles). Virucidal, post-treatment, and adsoption inhibition	[98]
	DENV-3	PLA2	Myotoxin-I (Mt-I)	*Bothrops asper*	Direct virucidal mechanism involving enzyme activity	[94]
			Myotoxin-II (Mt-II) PLA2 like	*Bothrops asper*	The same mechanism as Mt-I, although it exhibit weak antiviral effect (1000 times lower than Mt-I)	
			BlD-PLA2 (Asp49)	*Bothrops leucurus*	In addition to catalytic activity, the physiological role of BlPLA2s can be mediated by ligation to specific receptors on the cell membrane	[93]
			BlK-PLA2 (Lys49)	*Bothrops leucurus*	In addition to catalytic activity, the physiological role of BlPLA2s can be mediated by ligation to specific receptors on the cell membrane	
	HCV	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	direct virucidal mechanism	[29]
			PLA2-CB	*Crotalus durissus terrificus*	Inhibit HCV entry and replication and exhibit virucidal effect (Probable inhibition of gene expression related to lipid metabolism (DGAT, ACC, LDLr, and SREBP1c), resulting in challenges in viral particle assembly and subsequent block of replication).	[99]
			crotoxin (CX)	*Crotalus durissus terrificus*	Reduce virus entry and release with exhibition of virucidal effect	
			Crotapotin (CP) (subunits of CX)	*Crotalus durissus terrificus*	Inhibition of viral release	
	JEV	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Direct virucidal mechanism	[29]
	Rocio virus	PLA2	PLA2-CB	*Crotalus durissus terrificus*	Direct virucidal effect on virus particles	[92]
			crotoxin (CX)	*Crotalus durissus terrificus*		
	YFV	PLA2	Crotoxin	*Crotalus durissus terrificus*	The highest inhibitions of viral replication were observed in the virucidal, pre-treatment and adsorption assays indicating that the inhibition occurs at the initial steps of the replication cycle	[96]
			PLA2-CB	*Crotalus durissus terrificus*		
			PLA2-IC	*Crotalus durissus terrificus*		

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Table 1 (*continued*)

Virus families	Virus species	Family	Name of active compounds	Source	Antiviral properties	R
			rPLA2-CB1	*Crotalus durissus terrificus*	Virucidal activity	[97]
			rPLA2-CB2	*Crotalus durissus terrificus*		
			Myotoxin-I (Mt-I)	*Bothrops asper*	Direct virucidal mechanism involving enzyme activity	[94]
			Myotoxin-II (Mt-II) PLA2 like	*Bothrops asper*	The same mechanism as Mt-I, although it exhibit weak antiviral effect (1000 times lower than Mt-I)	
			BthTX-I	*Bothrops jararacussu*	antiviral activity in the virucidal, adsorption and internalization strategies	[96]
		SBPM	Crotamine	*Crotalus durrissus terrificus*	Low selectivity compared to crotoxin, crotapotin and PLA2-CB	[95]
	ZIKV	PLA2	BthTX-I	*Bothrops jararacussu*	mainly affect early stages of infections, inhibiting virus entry to the host cell. In addition to Interference with virus entry to the host cell.	[100]
			BthTX-II	*Bothrops jararacussu*	Same as BthTX-I, but SI Selectivity index 1000 times higher than BthTX-I	
			rPLA2-CB1	*Crotalus durissus terrificus*	Virucidal activity	[97]
			rPLA2-CB2	*Crotalus durissus terrificus*		
			(p-BthTX-I)2K	*Bothrops jararacussu*	Protect host-cells and inhibit virus in post-entry stage	[101]
		Cathelicidins	ZY13 (analog of BF-30)	*Bungarus fasciatus*	Antiviral activity *in vivo* and Direct inactivating ZIKV particles *in vitro* during preincubation and replication without acting on the virus attachement & strengthen the host antiviral immunity via AXL-SOCS (suppressor of cytokine signaling protein) pathway	[102]
Herpesviridae	HSV-1	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Direct virucidal mechanism	[29]
		Desintegrin	contortrostatin (with an Arg-Gly-Asp motif)	*Agkistrodon contortrix*	inhibitition of cell-to-cell fusion in HSV infection, polykaryocyte formation in HSV infection	[75]
Orthomyxo-viridae	H1N1	Cathelicidins	Cathelicidin BF-30	*Bungarus fasciatus*	worked on only the virus invasion stage, and inhibit the influenza virus infection by inhibit H1N1 and oseltamivir-resistant strain H1N1 and prevent fusion of the virus to the cell	[103]
	H3N2	Cathelicidins	Cathelicidin BF-30	*Bungarus fasciatus*	worked on only the virus invasion stage, and inhibit the influenza virus infection by prevent fusion of the virus to the cell	
	FLUAV	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Direct virucidal mechanism	[29]
Paramyxo-viridae	Sendai -virus SeV	metalloprotease	Echinhibin-1	*Echis coloratus*	inhibits the first vital step of the viral infection - the adsorption of the virions to the cells, probably by specific cleavage of the HN protein	[104]
		Crude venom [b]	Fraction C1	*Echis carinatus sochureki*	Similar to that of Echinhibin-1	[105]
		Crude venom	Fractions P3-P6	*Naja nigricollis*	Inhibit free virus and selectively lysis of erythrocytes that have been pre-infected with Sendai	[106]
		PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Weak antiviral activity	[29]

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Table 1 (*continued*)

Virus families	Virus species	Family	Name of active compounds	Source	Antiviral properties	R
	Measles virus	Crude venom	Cdt	*Crotalus durissus terrificus*	the MV infection was inhibited at the time of the initial events such as at the moment of adsorption and penetration of the viral cycle	[107]
Picornaviridae	Enterovirus A71	PLA2	MjTX-I	*Bothrops moojeni*	Demonstrated virucidal activity, could be acting on the pocket factor found in the depression of the EV-A71 capsid, destabilizing the virus particle	[108]
			MjTX-II	*Bothrops moojeni*	Demonstrated virucidal activity, could be acting on the pocket factor found in the depression of the EV-A71 capsid, destabilizing the virus particle. In addition to its action on replication level.	
			PLA2-CB	*Crotalus durrissus terrificus*	Inhibition of viral replication, could be the disruption of membranous replication organelles, abrogating virus replication.	[108, 109]
			CM-14	*Bothrops moojeni*	Block replication by virucidal effect	[109]
		SBPM	Crotamine	*Crotalus durrissus terrificus*	Demonstrated virucidal activity, could be acting on the pocket factor found in the depression of the EV-A71 capsid, destabilizing the virus particle. The antiviral activity of crotamin was observed on all steps of virus replicative cycle	[108, 109]
		SVSP	CM-10 (Moojase)	*Bothrops moojeni*	Block replication by virucidal effect	[109]
	Coxsackie-virus B3 (CV-B3)	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Weak antiviral activity	[29]
	Encephalomyocarditis virus (EMCV)	PLA2	CM-II-PLA2	*Naja mossambica mossambica*		
Reoviridae	Rotavirus	PLA2	Nh-PLA2	*Naja haje haje*	Virucidal activity: By interacting with the viral capsid, it may hinder the virus from attaching to host cells, thus inhibiting its spread.	[69]
Retroviridae	HIV-2	PLA2	crotoxin (CX)	*Crotalus durissus terrificus*	Inhibition of the viral entry without virucidal acitivity and preventing replication through acting on Gap p24	[28]
	HIV-1	PLA2	PLA2 OS2 (Venom) Recombinant OS2 WT OS2 K31L-R34S	*Oxyuranus scutellatus scutellatus*	Infectivity inhibitors without any indication about their action	[33]
			CM-II-PLA2	*Naja mossambica mossambica*	In acordance with action of Crotoxin, acting on viral entry without disrupting viral particles	[29]
			crotoxin (CX)	*Crotalus durissus terrificus*	Inhibition of the viral entry without virucidal acitivity and preventing replication through acting on Gap p24	[28]
			PLA2 NmmCMIII	*Naja mossambica mossambica*		[31]
			nigexine	*Naja nigricollis*		
			taipoxin	*Oxyuranus scutellatus*		
		LAAO	TSV-LAO	*Trimeresurus stejnegeri*	activating signal pathways in host cells which subsequently block viral replication and/or infection	[32]
		PLA2	HDP-1 HDP-2	*Vipera nikolskii* *Vipera nikolskii*	direct action on the virus, most likely due to the cleavage of glycerophospholipids on the viral envelope, which can lead to the destruction of the lipid bilayer and destabilization of the virus. The action is against different strains MvP-899, HIV-1 Zmb, HIV-2 EHO, and infectious molecular clones K3016 and AD8	[30]

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Table 1 (*continued*)

Virus families	Virus species	Family	Name of active compounds	Source	Antiviral properties	R
Rhabdoviridae	VSNJV	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Weak sensitivity	[29]
	Rabies virus CVS-11	Crude venom	P5-peptide (MW < 10 kDa)	*Naja naja oxiana*	It is assumed that the mechanism action of this peptide is by entering the cells through acetylcholine receptors and showed a high antiviral activity against pre-infected cells	[110]
Togaviridae	CHIKV	PLA2	rPLA2-CB1	*Crotalus durissus terrificus*	Virucidal activity	[97]
			rPLA2-CB2	*Crotalus durissus terrificus*		
			(p-BthTX-I)2K	*Bothrops jararacussu*	Act on early infection stages: attachement and internalization	[101]
	SINV	PLA2	CM-II-PLA2	*Naja mossambica mossambica*	Weak antiviral activity	[29]
	Mayaro virus MAYV	PLA2	PLA2-CB	*Crotalus durissus terrificus*	Direct virucidal effect on virus particles	[92]
			crotoxin (CX)	*Crotalus durissus terrificus*		

[a] PLA2 Family englobe both PLA2 and its homologs.
[b] Crude venom: unknown bioactive compound, and as a result, indeterminate family.

3. Results

3.1. Inhibiting HIV: anti-retroviral activity of snake venom compounds

Acquired immunodeficiency syndrome (AIDS) occurs when the immune system is weakened due to uncontrolled HIV infection [21]. HIV destroys $CD4^+$ T cells, which are the crucial for the immune function, through interactions of virus's envelope glycoprotein (gp120) and the $CD4^+$ of T cells. In addition to their interaction, the intervention of gp41, CCR5, and CXCR4, virus glycoproteins, and host cell receptors, respectively, ensure the entrance of the virus to the cells, followed by the integration into the human genome [22]. This mechanism primarily applies to the more common and virulent HIV-1 variant compared to the HIV-2 variant [23]. Although the emergence of an anti-HIV drug is necessary, there is neither vaccine nor a curing treatment for the disease [24]. According to the Joint United Nations Programme on HIV/AIDS 2022 (UNAIDS) report, the efforts to diminish the risk of HIV/AIDS are either on the wrong

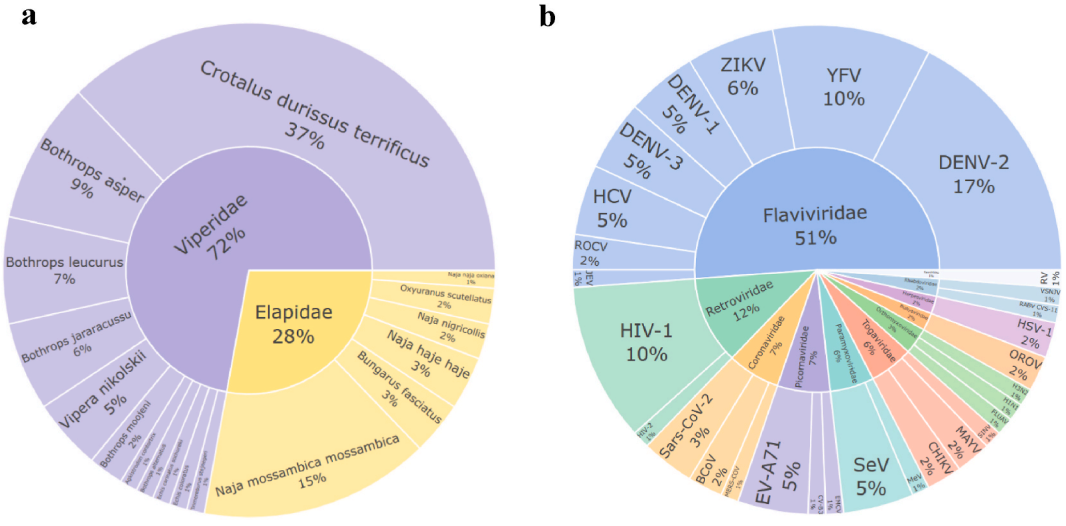

Fig. 1. Distribution of antiviral compounds in snake venoms across different families and species and their Efficacy Against various viruses.

track or moving insufficiently [25]. In 2021, an average of 1.46 million people were infected with HIV and 650 000 died from AIDS indicating the urgent need for action [25]. It is worth noting that more than 60 clinical trials for different HIV vaccines in phases I, II, or III, but none has been shown effective in stopping the disease [26,27]. Additionally, many attempts and more than 25 treatment agents under six different mechanisms of action have been tested for HIV, but none have resulted in patient cure, leaving all efforts so far fruitless [24]. Instead of curing the disease, lifelong therapy is suggested as a new direction [24].

The pie chart project all antiviral compounds on their source snake families and species **(a)** the proportion of these compounds derived from two major snake families: Viperidae and Elapidae, with a detailed breakdown of specific species like Crotalus durissus terrificus and Naja mossambica mossambica. And the effectiveness of these venom compounds against different viruses **(b)**, showcasing a broad spectrum of activity with a significant focus on the Flaviviridae family. Notably, DENV-2, YFV, and HIV-1 are the most significant targets, reflecting the potential of venom-derived compounds in therapeutic applications. Through the analysis, we have taken into account the same molecule when it has an impact on different viruses, even within the same families.

Overall, exploring new choices is needed to overcome this pitfall, such as the natural venom components therapy as fertile ground. Against this backdrop, *Retroviridae* (including HIV) is one of the top three virus families for which anti-viral compounds have been identified from snake venom (Fig. 1a). For instance, Crotoxin is the only snake venom protein that can inhibit both variants of HIV-1 and HIV-2 [28], while other snake venom proteins have been shown to only block HIV-1 [28–33]. Crotoxin is a heterodimer PLA2 complex and the major component in the venom of the South American rattlesnake *Crotalus durissus terrificus* [34]. In fact, the PLA2 proteins are the most described antiviral compounds among all snake protein families (Fig. 2). The basic PLA-CA (Component A, crotapotin) with high enzymatic properties and low toxicity, and the acidic PLA-CB (Component B) with enzymatic inactivity, both constitute subunits of the Crotoxin (CA-CB heterodimer). The inhibition mechanism of crotoxin consists of binding to the host cell membrane, hence, preventing the release of the major capsid protein p24 of HIV, which block the viral entry without acting on the interaction gp120-CD4 (Fig. 3) [28]. According to the same mechanism and without any direct virucidal effect, other PLA2s inhibit the HIV-1 variant through the prevention of the accumulation of the glycoprotein p24 in the cytosol, including tiapoxin and Nmm_{CMIII} from the snake venom of *Oxyuranus scutellatus* and *Naja mossambica mossambica*, respectively [31]. Along with tiapoxin and Nmm_{CMIII}, Nigexine showed a high affinity for the host cell membrane, leading to the supposition that the activity of these PLA2s is related more to the receptors of the host cell than their enzymatic properties [31].

On the other hand, some proteins found in snake venom exhibit potent anti-viral activity, but their mechanism of action remains unclear. For instance, PLA2 *Oxyuranus scutellatus scutellatus* toxin 2 (OS2) as well as the recombinant OS2 (rec OS2) produced through the expression of the wild-type in *E.Coli* and the double mutant OS2 (Lysine-31 and arginine-34 substituted by Leucine and Serine, respectively) named as OS2 K31L-R34S [33]. Those components showed an anti-viral potency without any clear indication of their mechanism of action. Chen et al., 2017 showed the broad inhibition range of the secreted phospholipase A2 CM-II isoform from *Naja mossambica mossambica,* including the anti-HIV-1 activity with an IC_{50} of 5.4 ng/ml [29]. The obtained results are in accordance with the above-described studies on the PLA2 family that inhibit HIV's entry without any virucidal effect. Recently, Siniavin et al. investigated the anti-viral potency of many PLA2 compounds from the snake venom of *Vipera nikolskii* [30]. Unlike the previously described mechanisms of PLA2 against HIV, Siniavin and colleagues demonstrated a direct virucidal activity of dimeric PLA2s HDP1 and HDP-2 due probably to the enzymatic properties of PLA2 [30]. In fact, Siniavin et al.'s investigation is consistent with the work of Kim et al.,

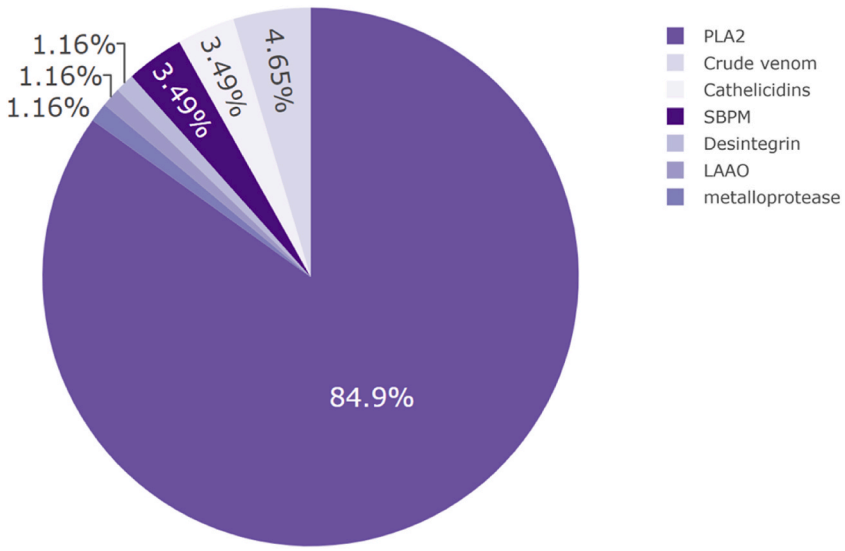

Fig. 2. Distribution of antiviral compounds in snake venoms across different protein or peptide families. The largest segment, by a significant margin, is PLA2, constituting 84.9 % of the composition. The other components, such as crude venom, cathelicidins, SBPM (Small Basic Polypeptide Myotoxins), disintegrin, LAAO (L-amino acid oxidase), and metalloprotease, are present in much smaller proportions, ranging from 1.16 % to 4.65 %.

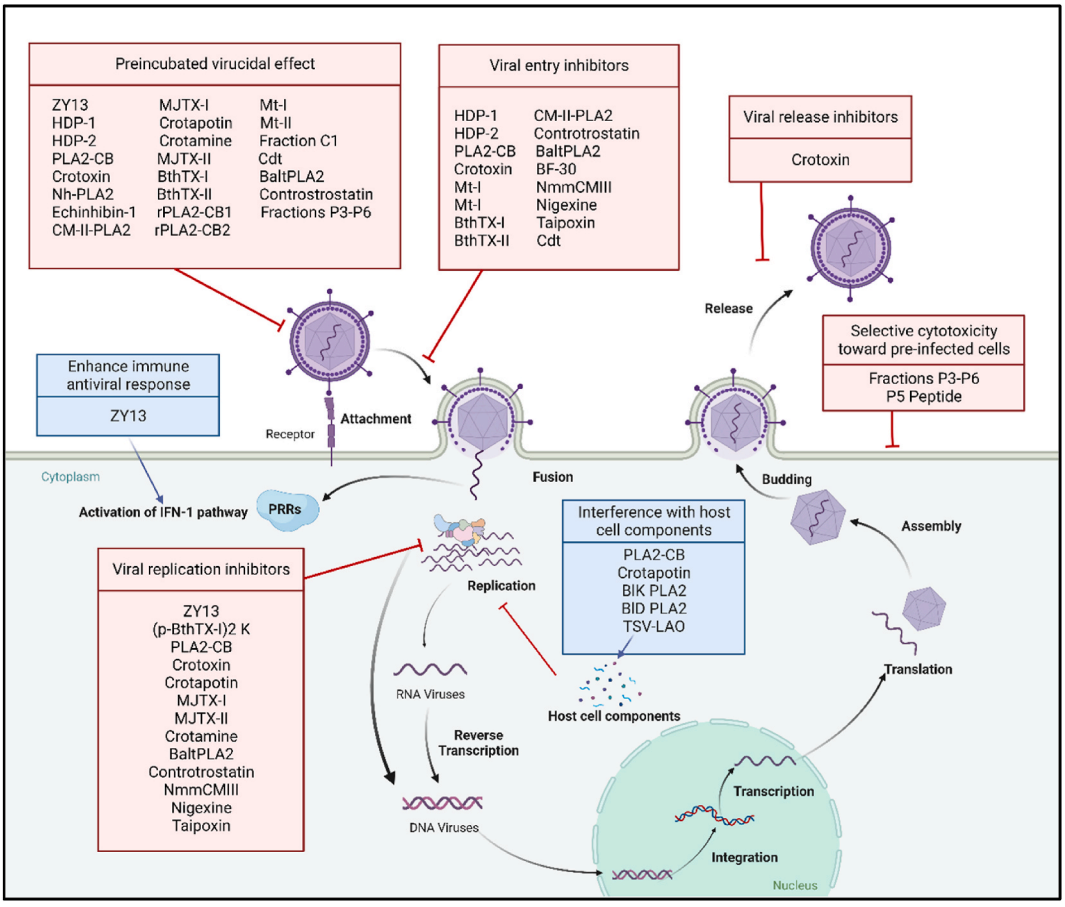

Fig. 3. Molecular targets and mechanism of action of antiviral compounds derived from snake venom in viral infections. The schema illustrates various phases in the life cycle of both RNA and DNA viruses, including, attachment of the virus to the host cell, membrane fusion, viral genome release, genome replication, reverse transcription, integration, transcription, translation, assembly, budding, and Virus release. Concurrently, it highlights diverse strategies employed by antiviral compounds derived from snake venom, encompassing, pre-virucidal effects, inhibition of viral entry, replication and release, selective cytotoxicity towards pre-infected cells, enhancement of immune antiviral responses, and interference with host cell components. Created with BioRender.com.

who showed the importance of enzymatic function during the anti-HIV activity of human sPLA2 (sPLA2-X) [35]. HDP-2 interferes with the virus in the early stages of the replication cycle of HIV-1, which block the replication of the virus (Fig. 3) [30]. Among the L-amino acid oxidase (LAAO) family, *Trimeresurus stejnegeri* venom (TSV-LAO), a protein found in the venom of the Chinese green tree viper *Trimeresurus stejnegeri*, is the only one with anti-viral activity [32]. TSV-LAO showed low toxicity and inhibits HIV-1 infection and replication through binding and activating the host cell [32]. LAAO enzymes catalyze the oxidation of L-amino acids to α-keto acids while releasing the hydrogen peroxide (H_2O_2) and ammonia. In fact, the generated H_2O_2 enhances the inhibition through activating signal pathways in host cells which subsequently block viral replication and/or infection [32]. It should be noted, however, that non-exogenous H_2O_2does not contribute to the enhancement of anti-viral activity [32]. LAAO enzymes have been reported from various organisms, including mammals [36], bacteria [37], algae [38], fungi [39], and insect venoms [40]. Furthermore, the snake venom LAAO (SV-LAAO) regarded as an attractive drugs source due to their apoptotic and cytotoxic (BpirLAAO-I, Lm-LAAO, and ACTX-8) [41–43], anti-viral [32], anti-microbial (MipLAAO, CC-LAAO, and Balt-LAAO-I) [44–46], anti-parasitic (BmarLAAO) [47], leishmanicidal (LAAO bordonein-L) [48] and anti-fungal activities (BmarLAAO, Th-L-AAO) [47,49]. Taken together, the LAAO family is a promising source of drugs with potential pharmaceutical and anti-viral applications to be further investigated.

3.2. *Anti-coronaviridae components from snake venom*

The *Coronaviridae* family, which belongs to the order *Nidrovirales*, is pathogenic and single-stranded, non-segmented, and positive sense RNA viruses (ssRNA+) with an envelope [50,51]. *Coronaviridae* affects different hosts and is characterized by its virion structure and the intracellular budding spot which set them apart from the other RNA viruses [52]. This family is divided into two sub-families: *Coronavirinae* and *Torovirinae*. *Coronavirinae* have an extended nucleocapsid with approximatively 60 kDa in size, while a tubular nucleocapsids of around 18 kDa for the *Toronavirinae*. *Coronavirinae* branched into four genera, including *Deltacoronavirus,*

Gammacoronavirus, Betacoronavirus, and *Alphacoronavirus* [53]. Coronaviruses (*Coronavirinae*), also called CoVs, known as the virus with the largest RNA genome (~30 kb) and can cause respiratory or intestinal illnesses in humans or animals [54,55].

Seven human coronaviruses (HCoVs) have been identified, with three (SARS-CoV, MERS-CoV, and SARS-CoV-2) causing severe diseases and significant outbreaks in the 21st century (2002, 2012, and 2019, respectively) [56,57]. The remaining four (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) typically cause mild infections such as the common cold [57]. Coronaviruses that can cause severe diseases are classified under the Beta-coronaviruses lineage [57]. Following the initial SARS-CoV and MERS-CoV outbreaks, the well-known Coronavirus Disease of 2019 (COVID-19) pandemic emerged. According to the WHO's statistics on the 24th December 2023**,** COVID-19 has globally affected over than 773 million people and resulted in 6 990 067 million deaths [58]. Although most patients have mild to moderate conditions and do not require advanced care, around 5–10 % of them suffer from severe to deadly illness [59]. Despite recent advances in vaccines and treatments, monotherapy strategies have showed a high failure rate, and there is a massive lack of approved and specific treatments that can cure the COVID-19 [60]. Therefore, it is crucial to identify efficient and effective anti-viral treatments against SARS-CoV-2, especially with the emergence of new variants that resistant to current treatments [61].

In this sense, the first report of a snake compound with anti-coronaviridae activity was published in 2017 for the broad-spectrum PLA2 isoform CM-II [29]. Despite the high anti-viral potency of PLA-CM-II against several viruses, this activity was low in the case of enveloped viruses such as MERS-CoV [29]. The spikes of this latter are large with a club-like or petal-like shape which may prevent the PLA-CM-II from attacking or entering to the lipid membrane of the virus [29,62]. Additionally, a dose-dependent inhibition assay suggested the division of MERS-CoV particles into two groups: sensitive (100 ng/ml) and resistance (10 000 ng/ml) [29]. Even though the budding site of *coronaviridae* is the ER-Golgi intermediate compartment (ERGIC) [62], there is a probability that the resistance group represents the particles in the plasma membrane which could be the reason for the lower inhibition effect of PLA-CM-II [29,63]. In 2021, two independent studies documented various PLA2-derived proteins and peptides with anti-SARS-CoV-2 activity [64,65].

Siniavin et al. conducted a study to investigate the anti-viral properties of eight PLA2s from the snake venom of *Vipera nikolskii, Vipera ursinii renardi,* and *Bungarus fasciatus* [65]. The results indicated that dimeric PLA2s HDP-1 and HDP-2 from *V. Nikolskii* and their subunits exhibit virucidal and anti-viral activity against SARS-CoV-2. The mechanism of action involves HDP-1 and HDP-2 acting as peptide fusion inhibitors that block the spike protein which prevents cell-cell fusion, while simultaneously destroying the viral membrane (virucidal effect). The catalytic fragment was found to be responsible for this mechanism, where the enzymatically active subunit (HDP-2P) exhibited two times higher inhibition activity than HDP-2. PLA2 HDP-2 demonstrated an anti-Bovine-Coronavirus (BCV) as well [65].

Meanwhile, peptides synthesized from C-Terminal of a homologous of PLA2 called Bothropstoxin-I (pBthTX-I) which was isolated from the snake venom of *Bothrops jararacussu* showed a broad-spectrum anti-microbial activity [66,67]. Interestingly, the degradation product of the serum: peptide (des-Lys12/Lys13-(p-BthTX-I)$_2$ demonstrated even higher anti-microbial activity [67]. Therefore, Freire et al. tested the anti-viral potency of des-Cys^{11}, Lys^{12}, Lys^{13}-(pBthTX-I)$_2$K, known as (pBthTX-I)$_2$K, and its analogs [64]. Subsequently, the examined peptides showed a micromolar low cytotoxic, high anti-viral effect, and high affinity to Papain-Like protease (PL^{Pro}). Their findings indicate that these peptides inhibit SARS-CoV-2 through the potential target PL^{Pro} [64].

Recently, complementary work has been done by Nogueira and colleagues to explore the anti-thrombotic effect of the anti-SARS-CoV-2 peptide (pBthTX-I)$_2$K [68]. As cardiovascular complications are the second side of COVID-19 infection and the main trigger of death through arterial and venous thrombosis. The *in vivo* study was conducted using a mouse model to investigate the anti-thrombosis effect of (pBthTX-I)$_2$K. The peptide was found to have an anti-thrombotic activity which resulted in less bleeding through the inhibition of Nitric Oxide (NO) [68]. Finally, *Naja haje* PLA2 (Nh-PLA2) is a PLA2 purified from the venom of *Naja haje* species. The protein showed an anti-viral activity based on virucidal tests, leading to the probable interpretation that it supressed the virus by blocking the attachment of the virus to the host cell through its binding with the viral capsid [69].

In addition to reported snake venom components with anti-SARS-CoV-2, the snake venom from *Naja Atra* (NNAV) and Cobrotoxin (an alpha-neurotoxin from NNAV) have been proposed as candidates to block the virus. Cobrotoxin and NNAV have various attractive criteria to suggest them as candidates, such as anti-inflammatory, analgesic, immunoprotective, lung protection, anti-viral, and safe properties [70]. Given that COVID-19 has been associated with cardiovascular complications, several reviews have introduced various snake venom components (in preclinical and clinical phases of other diseases) as potential candidates to treat COVID-19 patients [71–73]. These compounds include disintegrins, bradykinin-potentiating peptides (BBPs), and SVSPs, and they are believed to have mechanisms of action such as anti-pulmonary embolism, anti-coagulant, anti-thrombocytopenia, anti-thrombotic, anti-myocardial infarction, and other probable interventions [71,72].

Contortrostatin (CN) is a 13.5 kDa desintegrin disintegrin with an Arginine-Glycine-Aspartate fragment isolated from the venom of the eastern copperhead *Agkistrodon contortrix* with an integrin inhibition function [74]. CN has been found to inhibit the entry of viruses into cells, cell-to-cell fusion, and polykaryocyte formation, which can block HSV-1 (gL86) infection of various strains, including F, G, and MP; As result, CN act as a non-strain specific inhibitor [75]. The gL86 is a recombinant virus that has a portion of its gL gene replaced with the betagalactosidase instead of the 'lac Z' gene [76]. The synthesis of beta-galactosidase synthesis is associated with the successful entry and infection of the virus [76,77]. Therefore, the o-nitro-phenyl-b-d-galactopyranoside (ONPG) assay has been used to measure the expression of this enzyme. Subsequently, evidence of micromolar entry inhibition by CN has been established [75]. Furthermore, plaque assay was conducted on the pre-incubated HeLa cell lines with CN, and then the HSV-1 virus. which resulted in the inhibition of plaque formation. Thus, it is worth investigating the anti-SARS-CoV-2 potency of the Contortrostatin.

3.3. Anti-viral potency of snake compounds against Flaviviridae

Flavivirus, *Hepacivirus*, *Pegivirus*, and *Pestivirus* are the four genera of the *Flaviviridae* family [78]. Like *Retroviridae* and *Coronaviridae*, *Flaviviridae* is a small enveloped viruses with a ssRNA + genome (9–13 kb); additionally, various pathogenic species branching under this family, such as *Dengue virus, HCV, and Bovine Viral Diarrhea Virus (BVDV)* who belongs to *Flavivirus*, *Hepacivirus*, and *Pestivirus*, respectively [78,79]. The primary hosts of this virus family are mammals and birds, mainly transmitted through arthropod vectors, such as mosquitoes and ticks. The *Flavivirus* genera comprises over 70 viruses [78]. Based on their insect vector, the flaviviruses could distinguish mosquito-borne, tick-borne, and viruses with unknown vectors [80]. As a source of various human diseases, *Flaviviridae* has been extensively studied [79]. Within the *Flavivirus*, West Nile virus (WNV), yellow fever virus (YFV), DENV, Japanese encephalitis virus (JEV), and tick-borne encephalitis virus (TBEV) are known as viruses that cause major health problems [81]. For instance, liver and kidney damage (YFV), neurological sequelae (JEV, ZIKV, and TBEV), liver cancer and diseases (HCV), and encephalitis (WNV) are major diseases caused by the *Flaviviridae* virus family [80]. Each year, up to 400 million people worldwide are infected by Dengue viruses alone (DENV1-4) [82]. Whereas HCV, as a member of the *Hepacivirus*, is well-explored as a global health problem on the rise, affecting an estimated 2–3% globally, more than 130 million people [83]. In terms of flaviviruses vaccination, only five vaccines have been approved against YFV, JEV, DENV, tick-borne encephalitis virus (TBEV), and Kyasanur forest disease virus (KFDV) [84–88]. In addition to the critical importance of developing new vaccines for these viruses to control their emergence and re-emergence [82], there is a huge lack in the side of pathogen-specific anti-virals without any approved medications to treat flaviviruses infections [89–91]. In this regard, investigating other promising and new fields, such as the active components of snake venom, could cover the deficiency of therapeutics.

Among virus families, *Flaviviridae* is widely recognized as having been extensively explored in developing anti-viral compounds based on snake venom (51 %) (Fig. 1b). Researchers have reported anti-viral activity against *Flaviviridae* viruses: DENV 1–3, HCV, JEV, YFV, ZIKV, and Rocio (ROCV) (Table 1).

Among the arthropod-borne diseases, Dengue fever (DF) is the most common disease caused by Dengue virus (DENV), mainly transmitted by *Aedes aegypti* mosquito [111]. Four distinct types of DENV named from 1 to 4 (phylogenetically and anti-genically differ) can cause mild, moderate to severe illnesses with a higher risk to infect people living in tropical area (<3.6 billion people), leading to the death of approximately 20 000 deaths per year [112]. In addition to DF, the virus can lead to dengue shock syndrome (DSS), dengue hemorrhagic fever (DHF) and asymptomatic infections, with DHF/DSS the most severe form [112].

The mechanism of action of snake venom components against viruses vary, even within the same protein family, such as PLA2. One of these mechanisms involves interfering with the host cell components to prevent virus replication or entry. With the latter described mechanism, two PLA2 from the snake venom of *Bothrops leucurus,* known as BlK-PLA2 and BlD-PLA2, inhibit the DENV1, 2 and 3 [93]. The main differences between those PLA2 are the amino acid of the position 49 (lysine for BlK-PLA2 and aspartic acid for BlD-PLA2), the number of amino acids (121 for BlK-PLA2 and 122 for BlD-PLA2), and phospholipase activity (negligible for BlK-PLA2 compared to BlD-PLA2) [113]. The anti-viral activity of these proteins (Bl-PLA2) could be related to their enzymatic activity (especially BlD-PLA2) or their pharmacological domains, or both [93].

Meanwhile other proteins exhibiting a virucidal activity against viruses, including Myotoxin (Mt-I), Myotoxin (Mt-II), BthTX-1 and 2, CM-II-PLA2 and others. For instance, Mt-I a catalytically active PLA2 and Mt-II a homologue of PLA2, are PLA2 proteins extracted from the snake venom of *Bothrops asper*. In nanomolar concentration, Mt-I and Mt-II inactivate various Flaviviridae viruses, including DENV serotypes 1 to 4 and YFV, through virucidal activity rely on the enzymatic properties, which explain the one-thousand-fold lower efficiency of Mt-II (PLA2-like) compared to Mt-I (PLA2) [94]. Although the activity has been tested against non-enveloped and enveloped viruses, Both PLA2 proteins showed a bias inhibition towards enveloped Flaviviridae viruses compared to others enveloped viruses such as HSV-1, HSV-2, Influenza A H3N2, and Vesicular stomatitis VSV (strains: Indiana and New Jersey) and non-enveloped viruses (Sabin Poliovirus 1,2 and 3) [94]. From the same genus (*Bothrops*) but another species (*Bothrops jararacussu*), Bothropstoxin I (BthTX-I) a PLA2 without any phospholipasic activity showed an anti-viral activity with low selectivity index compared to crotoxin, PLA2-CB, and PLA2-IC [101]. BthTX-I inhibit DENV-2 and YFV through various intervention including virucidal, adsorption and internalization, although its high myotoxic activity in mice and its cytotoxicity in VERO E6 cells [101]. Recently, an independent study demonstrated the anti-ZIKV activity of those bothropstoxins (BthTX-I and BthTX-II) through a virucidal effect mostly in the early phases of virus replication. Although both proteins are myotoxins, the BthTX-II is catalytically active with an anti-viral activity associated with a Selectivity Index (SI) 1000 times higher than BthTX-I which could refer to the presence of enzymatic activity [102]. Balt-PLA2 (*Bothrops alternatus*), a PLA2 enzymatically active, has been reported for its virucidal activity against Dengue virus type 2 [98]. Additionally, CM-II-PLA2 induce a nanomolar virucidal effect against HCV, DENV, and JEV as Flaviviridae and other enveloped viruses due probably to their budding through the endoplasmic reticulum and low anti-viral activity against other viruses (Table 1) [29].

The South American snake *Crotalus durissus terrificus* reported as rich source of anti-viral and anti-Flaviviridae compounds including Crotoxin (CX), Crotapotin (CP), PLA2-CB, recombinant PLA2-CB (rPLA2-CB), Crotamine, and PLA2-IC [92,96,97,99]. Muller et al. showed the anti-DENV-2 and anti-YFV activities of CX, PLA2-CB and PLA2-IC via various assays including virucidal, pre-treatment and adsorption which reveal their intervention in the initial phases of replication cycle of the viruses [96]. Afterward, they demonstrated the direct destruction effect of dengue virus by PLA2-CB and crotoxin and inhibiting other viruses including Rocio virus [92]. The author and colleagues presumed that the entry of PLA2 proteins to lipid bilayer membrane happened via pores that located on the 3-fold vertex of the E protein, hence, cleaving glycerophospholipids on the virus envelope which led to the destabilization of the envelope proteins, therefore virus neutralization [92]. In accordance with the same mechanism, CX, CP and PLA2-CB inhibit HCV replication, most likely via reducing the expression of lipid metabolism genes which prevent assemblance and

replication of viral particles and could also related to the phospholipase activity of PLA2-CB [99,114]. In addition to their effect on host cell metabolism genes, it could be coupled with an inhibition of virus entry (PLA2-CB and CX), replication (PLA2-CB), or release (CX and CP) [99]. Subsequently, two isoforms of PLA2-CB have been produced using E.Coli BL21 as an expression factory named as recombinant PLA2-CB (rPLA2-CB1 and rPLA2-CB2) [97]. Both isoforms showed a virucidal activity against Flaviviridae viruses including DENV-2, YFV, and ZIKV and a Togaviridae virus (Chikungunya Virus briefly CHIKV) [97]. The observed half effective concentration (EC_{50}) in virucidal assay and cytotoxicity concentration (CC_{50}) of recombinant isoforms were higher than native PLA2-CB. Specifically, EC_{50} values were 240–260 ng/μL and 0.01647–0.044 ng/μL, while CC_{50} values were 10.03–14.74 μg/μL and <0.5 μg/μL for rPLA-CB2s and PLA2-CB, respectively. The lower virucidal properties and the higher cytotoxicity of recombinant proteins could be explained by their lower phospholipase activity and the presence of the detergent 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate hydrate (CHAPS), respectively [97].

From the restricted list of snake peptides that possess anti-viral properties, ZY13 and Crotamine are isolated from *Bungarus fasciatus* and *Crotalus durrissus terrificus* with potential to inhibit ZIKV and both YFV and DENV-2, respectively [95,102]. ZY13 an analog of Cathelicidin-BF-30 (BF-30) with hydrophobic polarity and 15-amino acids. BF-30 is a defensive peptide from the snake venom of *Bungarus fasciatus* which regarded as an excellent model to develop therapeutic peptides [102]. In this regard, BF-30 and its analogs were authorized in clinical trials (phase I-III) under the approval number CXHL1700235 for anti-microbial usage (vaginitis) [102]. Subsequently, the micromolar anti-viral activity of BF-30 against the Orthomyxoviridae family has been demonstrated, including H3N2, H1N1, and the strain of H1N1 that resist to Oseltamivir [103]. The activity has been proved *in vitro* and *in vivo*, via the intervention of BF-30 on virion membrane fusion, without acting on the viral proteins hemagglutinin-neuraminidase [103]. Thereafter the potential of ZY13 (the analog of BF-30) to directly disactivate ZIKV virions and increasing the host immune response to the virus infection [102]. On the other hand, the pre-treatment of VERO E6 cells with Crotamine showed an inhibition of 20 % and 11 % and the post-treatment inhibition was 9 % and 25.2 % for the YFV and DENV-2 viruses, respectively, in the tested concentrations ranging from 12.5 to 100 ng/μL [95]. The peptide isolated from the crude venom of *Naja naja oxiana* with anti-Rabies virus properties is the last peptide to be mentioned in the list of peptides discussed in this review [110]. The study showed that the P5 peak of the crude venom of *N. n. oxiana* corresponds to a peptide with a molecular weight less than 10 kDa. The proposed mechanism of action of the P5 on CVS-11 strain of rabies virus consist of the entry of the peptide to host cell through acetylcholine receptors, hence, interfering with the virus in post infection level [110].

3.4. Anti-Paramyxoviridae potency of snake venom proteins

Paramyxoviridae is a host-specific, negative-sense, enveloped and large RNA viruses (14.6–20.1 kb), infecting various animals (fish, birds, reptiles, and mammals) and humans [115]. The most known *Paramyxoviridae* viruses that lead to human diseases are respiratory syncytial virus (RSV), Nipah virus, Hendra virus, Mumps virus, Measles virus (MV) and some parainfluenza viruses [115]. Paramyxoviruses commonly known as inducer of severe respiratory diseases during childhood and associated with higher threating to develop an asthma [116,117]. *Paramyxoviridae* possess unique connections with *Orthomyxoviridae* and *Rhabdoviridae* families due to the characteristics of the glycoprotein envelope and the similarity of the organization and the expression of the non-segmented genome, respectively [118]. Sendai virus (SeV) also called mouse parainfluenza virus type 1, can cause respiratory diseases, and belongs to the parainfluenza viruses [118]. The latter consider as one of the most prevalent viruses and englobe various species including *human parainfluenza viruses type 1 to 5*, where serotype 1 and 3 belongs to genus *Respirovirus* and type 2, 4 and 5 are members of *Rubulavirus* genus [118]. MV among the most infectious and prevalent viruses [118].

Echinhibin-1, fraction C1 of crude venom, and fractions P3-P6 of crude venom, as well as CM-II-PLA2 from the venom of *Echis coloratus, Echis carinatus sochureki, Naja nigricollis,* and *Naja mossambica mossambica* have demonstrated anti-SeV activity [29, 104–106]. CM-II-PLA2 exhibited a minimal neutralization effect against SeV, with a half inhibitory concentration less than 10 000 ng/ml as the case of SINV and FLUAV which explained by their budding site [29]. Echinhibin-1 is a metalloprotease that eradicates the virus at 1 μg/mL and 10 μg/mL in an incubation of 24 h and 2 h, respectively [104]. The glycoprotease act on the first of the viral infection through blocking adsorption of the virion to the cells which could referred to the cleavage of hemagglutinin-neuraminidase (HN) protein [104]. The fraction C1 act as a metalloprotease and exhibited a micromolar inhibition properties against the hemolytic activity of SeV (IC_{50}: 1.25 μg/ml) [105]. The mechanism of C1 is quite similar to that of Echinhibin-1 as they both share a common ancestral genus; hence, it could also lead to destruction of viral virions such as HN protein [105]. The four cytotoxins (P3-P6) from *Naja nigricollis* have been found to inhibit free virus and selectively lyse erythrocytes that have been pre-infected with Sendai. This suggests that the cytotoxins can specifically target and destroy virus and virus-infected cells, without harming unaffected cells [106]. In the case of MV, the crude venom of *Crotalus durissus terrificus* (Cdt) have been demonstrated a blockage of the viral replication before and within the infection of the Vero cells with the virus and less efficient after the infection [107]. The inhibition observed in the concentration 0.1–100 μg/ml without any cytotoxicity and the interaction between Cdt and the external subunit could be the initiated checkpoint of the inhibition.

3.5. Broad-spectrum anti-viral effects of snake venom components

The anti-viral potency of snake compounds has been reported against other families of RNA viruses including *Bunyaviridae* (Oropouche virus), *Picornaviridae* (Enterovirus A71, Coxsackievirus B3, and encephalomyocarditis virus), *Reoviridae* (Rotavirus), and *Togaviridae* (CHIKV, Sindbis virus, and Mayaro virus).

Bunyaviridae is a negative single-stranded RNA viruses, englobe 4 genera, 35 serotypes and 304 types and subtypes [119]. The

family consider as a root of various diseases such as fevers, renal failure, blindness, and hemorrhagic hepatitis in animals and humans [119]. Oropouche virus (OROV) is a common arthropod-borne diseases especially in Amazonia. The disease causes symptoms that similar to other arboviral diseases like Mayaro, Dengue, Chikungunya fevers, this ambiguous distinguish lead to uncertain estimation of the infected patients [120]. The lack of efficient diagnostic tools and the absence of specific anti-viral medicines reflect the importance to deal with the current health problem [121]. In this regard, PLA2-CB and crotoxin have been reported as inhibitors of OROV with the same action as DENV through a direct action on the OROV particles [92]. The EC_{50} values for PLA2-CB and crotoxin, against OROV, are 0.0067 ng/μL and 0.0054 ng/μL, respectively [92].

Thought the high prevalence of *Picornaviridae* infections, most of them failed to show any symptoms and can affect different organs and systems including respiratory system, liver, skin, pancreas, heart, eye, and digestive tract [122]. The non-enveloped EV-A71 virus is one of the *Picornaviridae* viruses that cause mouth, foot, and hand disease and could accompanied with severe neurological effects, predominantly observed in children residing in the Western Pacific area [123]. Despite the high morbidity and mortality rates associated with the EV-A71 viral infection, there are no approved treatments for enterovirus infections [124]. Regarding the case coxsackievirus B3 (CV-B3) and encephalomyocarditis virus (EMCV), CM-II-PLA2 have been failed to neutralize them despite the high dose as 10 000 ng/ml [29]. On the other hand, four toxins from the venom of two different snakes; *Bothrops moojeni* (MjTX-I and MjTX-II) and *Crotalus durissus terrificus* (PLA2-CB and Crotamine) demonstrated an anti-Enterovirus A-71 (EV-A71) potency [108]. In the case of PLA2-CB that showed an inhibition of the viral replication noted during a post-entry assay (89 % of inhibition), an interfering with membranous replication organelles (2B,2C and 3A) and EV-A71 replication is proposed as mechanism of action. Whereas Crotamin, MjTX-I and II could targeting hydrophobic pocket in the virus capsid which dysregulate the stability of the virus particles [108].

Among the fifteen genera of the *Reoviridae* family that affect a wide range of organisms (protozoa, fungi, plants, animals, and humans), rotaviruses are one of the pathogenic viruses that leads to gastroenteritis in both animals and humans. In addition to the contribution of rotaviruses in childhood gastroenteritis, it is the primary source of illness and death among infants in developing countries [125]. A member of the *Reoviridae* family, named as Rotavirus and classified under the most contagious enteropathogens leading to severe gastroenteritis among animals, children, and infants [69]. Currently, there is a no anti-rotavirus drugs, hence investigating other fields is crucial [69]. In this context, the purified PLA2s of *Naja haje* have been shown the potency to block simian rotavirus (RV SA-11) *in vitro* with a reduction of viral titers by 2.5 log10 TCID50 [69].

Togaviridae is a +ssRNA virus family that significantly contribute to human illnesses and divided into two genera *Alphavirus* and *Rubivirus* [126]. The former is the largest genus causing various diseases such as rash, fever, encephalitis, and arthritis due mainly to arthropod vectors. SINV one of alphavirus genus that has been widely explored due to the ease of cultivation in cell culture and its potency to cause mild to asymptomatic human diseases [126]. Due probably to the budding site of SINV, CM-II-PLA2 couldn't neutralize the virus. In revenge, Mayaro virus (MAYV) have been neutralized with PLA2-CB and crotoxin due to a direct virucidal potency [92]. Similarly, CHIKV have been blocked due to the recombinant isoforms (rPLA2-CB1 and rPLA2-CB2) [97].

4. Conclusion

The danger of viral infections isn't limited to humans only, but plants and animals as well, causing human health problems, corruption of agricultural crops, and affecting domestic animals. The threat of viruses related also to their ability to cross species, as the well-known case of SARS-CoV-2 that transmitted from pangolin to humans which led to a global pandemic. The described viruses cause zoonoses (zoonotic diseases) and represent an estimation of 75 % of new emerging infectious illnesses (3 out of 4). Taken together, this highlights the danger of emergent diseases, where viruses are the major cause of both emergence and the re-emergence, posing global threats due to their rapid spread and high mutation rate. The impact of viral diseases including the case of pandemic, epidemic and outbreaks surpasses disrupting of healthcare systems to the economic impact such as job losses, limited tourism, and less active communities. Considering these hazards, it is imperative to invest more on vaccination programs and therapeutics research, especially in the absence of specific medicines in the case of most viruses. Therefore, nature consider as the first choose to open the door on possible and new treatments from plants, animals, and bacteria. Within this framework, recent advancements in high-throughput technologies help us to investigate the most complex and the limited amounts of drug sources as the situation of snake venom. The importance of snake venom as drugs repertoire is related to the high variation in its composition among species and within the same species.

The snake anti-virals act on various levels of virus including inhibition of virus entry (e.g. crotoxin), blockage of viral replication (e.g. PLA2-CB), interfering with viral release (e.g. crotoxin), virucidal potency (e.g. Mt-I), protection of host cells (e.g. crotamin), enhancing host immunity against viral infections (e.g. ZY13), and unknown mechanism of actions (e.g. PLA2 OS2). The anti-virals protein families aren't restricted to the widely known PLA2 family, but also and in a small portion other families including Cathelicidins, Desintegrin, Metalloprotease and LAAO, which reflect the necessity to investigate the anti-viral potency of those families and many others. Exploring their analogs and testing the recombinant expression of snake derived proteins may increase their effectiveness against viruses as applicable to (p-BthTX-I)2 K in action against SARS-CoV-2 and ZY13 against ZIKV. Accelerating research on this field could offer a whole new opportunity to treat various diseases in case we succeed in moving from *in vitro* to more *in vivo* assays, hence, clinical assays. For this purpose, we need to understand the structure-function relationships, screen large snake venom libraries with high-throughput technologies, probe pharmacokinetics activities like 'absorption, distribution, metabolism, excretion and toxicity' (ADMET), minimizing off-target effects through targeted drug delivery systems such as nanoparticles which allow us to identify the real influence of toxins, and integrating machine learning to predict the anti-viral activity of snake venom compound. While snake venoms contain molecules with antiviral properties, the transition to clinical phases requires rigorous validation. In this regard, there is

very limited clinical assay of antivirals based on snake venom, which raises questions about efficiency and the issues related to this drug source, especially reasons that prevent this transition. Probably the main reason behind the difficulty in ensuring advancement is related to the very limited studies in that field, contrary to small molecules from plants, for example, and the high molecular weight compared to the compounds from scorpion venom, especially for large-scale production. Studies in this field are on an increasing trend, which could be promising and would open the door to all issues related to these compounds. In 2008, a case was reported for the utilization of a combination of compounds from snake venom in conjunction with antiretroviral therapy for an HIV patient resistant to multidrugs, which showed positive results, including a remarkable decrease in viral load and an increase in CD4 cells [127]. This case is believed to be the first and the only clinical study where venom compounds have been utilized to treat a viral disease, with a result of the addition of venom compounds without any adverse effects. However, one case cannot reflect the safety and efficacy of viral compounds *in vivo*. All of this emphasizes the need for further research to ensure safety and efficacy before moving on to the clinical phase.

Data availability

All collected data are included in Table 1 of the article.

CRediT authorship contribution statement

Hicham Hboub: Writing – review & editing, Writing – original draft. **Reda Ben Mrid:** Writing – review & editing, Writing – original draft. **Najat Bouchmaa:** Writing – review & editing, Writing – original draft. **Naoual Oukkache:** Writing – review & editing, Writing – original draft. **Rachid El Fatimy:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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