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Role of Phospholipases A2 as Anti-Covid 19

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Abstract – In this review trial has been made for the search of anti-covid 19, so my idea depends on the choice of phospholipases A2 as anti-covid 19 depending on the following evidences:
Phospholipases (PLs) are a ubiquitous group of enzymes that share the property of hydrolyzing a common substrate, phospholipid. Nearly all share another property; they are more active on aggregated substrate above the phospholipid's critical micellar concentration (cmc). Phospholipases have low activity on monomeric substrate but become activated when the substrate concentration exceeds the cmc. The phospholipases are diverse in the site of action on the phospholipid molecule, their function and mode of action, and their regulation. The diversity of function suggests that phospholipases are critical to life since the continual remodeling of cellular membranes requires the action of one or more phospholipase. Their functions go beyond their role in membrane homeostasis; they also function in such diverse roles from the digestion of nutrients to the formation of bioactive molecules involved in cell regulation. There are indications that a few phospholipases may carry out a biological function independent of their catalytic activity by binding to a regulatory membrane receptor. Phospholipase-like proteins with toxic properties, yet which lack a functional catalytic site, are found in venoms. It is of interest that most, but not all, phospholipases studied in detail thus far are soluble proteins. The soluble nature of many phospholipases suggests that their interaction with cellular membranes is one of the regulatory mechanisms that exist to prevent membrane degradation or to precisely control the formation of phospholipid-derived signaling molecules. The classification of the phospholipases based on their site of attack. The phospholipases A (PLAs) are acyl hydrolases classified according to their hydrolysis of the l-acyl ester (PLAI) or the 2-acyl ester (PLA2). Some phospholipases will hydrolyze both acyl groups and are called phospholipase B. In addition, lysophospholipases remove the remaining acyl groups from monoacyl (lyso) phospholipids. Cleavage of the glycerophosphate bond is catalyzed by phospholipase C (PLC) while the removal of the base group is catalyzed by phospholipase D (PLD). The phospholipases C and D are therefore phosphodiesterases [5].

Keywords – Phospholipases A2, Anti-Covid 19, Covid 19.

I. INTRODUCTION

On December 31, 2019, the China Health Authority alerted the World Health Organization (WHO) to several cases of pneumonia of unknown an etiology in Wuhan City in Hubei Province in central China. The cases had been reported since December 8, 2019, and many patients worked at or lived around the local Human Seafood Whole sale Market although other early cases had no exposure to this market **[1]**. On January 7, a novel coronavirus, originally abbreviated as 2019-nCoV by WHO, was identified from the throat swab sample of a patient **[2]**. This pathogen was later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group **[3]** and the disease was named coronavirus disease 2019 (COVID-19) by the WHO. As of January 30, 7736 confirmed and 12,167 suspected cases had been reported in China and 82 confirmed cases had been detected in 18 other countries **[4]**. In the same day, WHO declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC) **[4]**. In this review trial has been made for the search of anti-covid 19, so my idea depends on the choice of phospholipases A2 as anti-covid 19 depending on the following evidences:

Phospholipases (PLs) are a ubiquitous group of enzymes that share the property of hydrolyzing a common substrate, phospholipid. Nearly all share another property; they are

more active on aggregated substrate above the phospholipid's critical micellar concentration (cmc). Phospholipases have low activity on monomeric substrate but become activated when the substrate concentration exceeds the cmc. The phospholipases are diverse in the site of action on the phospholipid molecule, their function and mode of action, and their regulation. The diversity of function suggests that phospholipases are critical to life since the continual remodeling of cellular membranes requires the action of one or more phospholipase. Their functions go beyond their role in membrane homeostasis; they also function in such diverse roles from the digestion of nutrients to the formation of bioactive molecules involved in cell regulation. There are indications that a few phospholipases may carry out a biological function independent of their catalytic activity by binding to a regulatory membrane receptor. Phospholipase-like proteins with toxic properties, yet which lack a functional catalytic site, are found in venoms. It is of interest that most, but not all, phospholipases studied in detail thus far are soluble proteins. The soluble nature of many phospholipases suggests that their interaction with cellular membranes is one of the regulatory mechanisms that exist to prevent membrane degradation or to precisely control the formation of phospholipid-derived signaling molecules. The classification of the phospholipases based on their site of attack. The phospholipases A (PLAs) are acyl hydrolases classified according to their hydrolysis of the l-acyl ester (PLAI) or the 2-acyl ester (PLA2). Some phospholipases will hydrolyze both acyl groups and are called phospholipase B. In addition, lysophospholipases remove the remaining acyl groups from monoacyl (lyso) phospholipids. Cleavage of the glycerophosphate bond is catalyzed by phospholipase C (PLC) while the removal of the base group is catalyzed by phospholipase D (PLD). The phospholipases C and D are therefore phosphodiesterases **[5]**.

II. Phospholipases A2: Structure And Function

The phospholipases (A1, A2, Cand D) are a complex and crucially important group of enzymes that hydrolyse phospholipids, releasing a variety of products depending on the site of hydrolysis (Fig.1). Phospholipases A2 (PLA2) refers to the enzymes that cleave the *sn*-2 position of phospholipids to generate the corresponding fatty acid and lysophospholipid. Perhaps the most important fatty acid that is released is arachidonic acid, the precursor of a variety of downstream signaling molecules (eicosa- noids) including prostaglandins and leukotrienes. In addition, the lysophospholipids such as lysophosphatidyl choline can play an important role as signaling molecules in their own right or are the precursors of signaling molecules such as platelet-activating factor (PAF). The normal phospholipid substrate for phospholipases is an amphipathic molecule with a critical micelle concentration (CMC), which is subnanomolar. These phospholipids self-assemble into aggregates within the body, such as the bilayer of biological membranes, or become the monolayer coat of the blood lipoproteins. In the intestine, phospholipids are found in mixed micelles with bile acids. As a result of phospholipid aggregation and the very low CMC of phospholipids composed of long-chain fatty acids, monomeric phospholipid molecules in solution are present at an extremely low concentration.

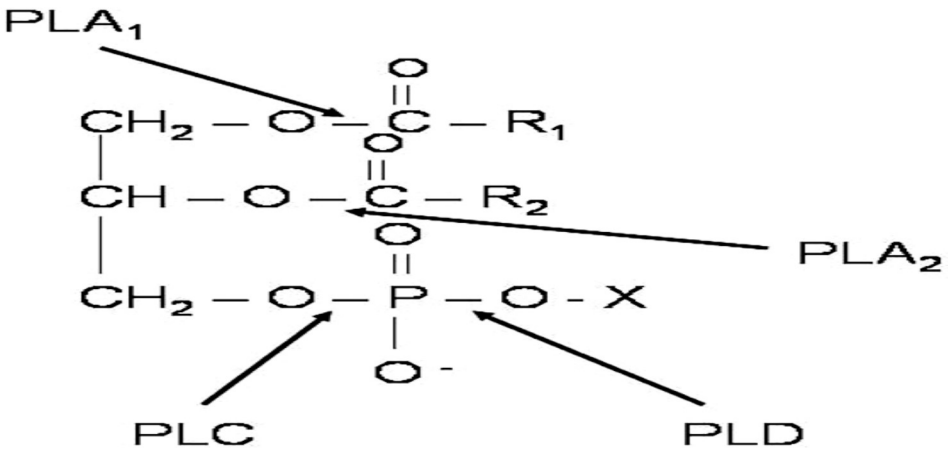

Figure1. Sites of hydrolysis by phospholipases

An important corollary of the overall scheme for interfacial binding is that if the enzyme cannot bind to the interface, phospholipid hydrolysis cannot occur. The enzyme may remain bound to the membrane surface during many catalytic cycles (scooting) or dissociate from the interface with each cycle (hopping) **[5, 6]**. Interfacial binding is an additional parameter when describing the properties of such enzymes and plays a crucial role in regulating enzyme activity within the body. Much of phospholipase research at the molecular level is directed towards understanding the molecular basis and regulation of interfacial binding. The research on PLA2 enzymes has its origins in the abundant digestive enzymes of the pancreas and a wide variety of snake venoms. These enzymes were flow molecular weight (14 kDa) and were secreted from cells. They were not able for being stable molecules containing a large number of disulphide bonds, consistent with working in a n extracellular environment, and required a high concentration (mM) of Ca21 for optimum catalytic activity. In more recent years, these abundant low molecular weight enzymes have been supplemented by an increasing number of non-digestive secreted enzymes that function within the body and can be linked with the inflammatory response. In addition, the PLA2 now also include a wide variety of other enzymes of very different structures that are involved in phospholipid remodeling and cell signaling They make up a total of 12groups with diverse structures, functions and catalytic mechanisms. The classification of such groups has been detailed **[7]**.

In this review we will discuss this family of enzymes according to the group classification. The review will be restrictedtoclassicalPLA2 that release long chain fatty acids from membrane phospholipids; another important group of PLA2, the PAF acetyl hydrolyses **[6]**, will not be discussed. Historically, it was the abundant secreted enzymes from pancreatic juice and venoms that dominated our under-standing of such enzymes for many decades. These proteins were classified as group I, II and III enzymes, a classification that was refined to reflect detailed structure and further information about a wide range of venom enzymes **[7, 8]**. For example, the enzymes derived from the pancreas are now called group IB enzymes, while the bee venom enzyme is in group III. In thelater1980's, a second mammalian PLA2 was isolated and identified from platelets and other immune cells, and found in the synovial fluid of patients with rheumatoid arthritis. The major effort in cloning and expression of this low-abundance groupie A enzymein1989,followed by detailed investigations, was encouraged by the belief that this non-pancreatic enzyme was responsible for catalyzing the release of arachidonic acid in cells, which is the rate limiting step in eicosanoid production **[9]**. However, in 1991, a novel high-molecular weightPLA2 (85 kDa) was purified from the cytosol of various cells. This enzyme had the properties that would be anticipated for aPLA2 that was involved in arachidonic acid production within the cell, including a high specificity for arachidonic acid at the *sn*-2 position of the phospholipid **[10]**. The enzyme is known ascytosolicPLA2 and is classified as group IV. Since that time, a number ofPLA2 have been identified, including agroupVICa21-independent PLA2 **[11]**, and these have been classified within groups I–XII. In this review, the PLA2 will be dealt with according to classification, but taking not of the structural and functional similarities between certain groups. As a result, it is normal to subdivide classical PLA2 into three categories, secretedPLA2 (sPLA2), cytosolicPLA2 (cPLA2) andCa21- independent PLA2 (iPLA2)

III. Broad-spectrum antiviral agents: secreted phospholipase A2 targets viral envelope lipid bilayers derived from the endoplasmic reticulum membrane

Hepatitis C virus (HCV), dengue virus (DENV) and Japanese encephalitis virus (JEV) belong to the family *Flaviviridae*. Their viral particles have the envelope composed of viral proteins and a lipid bilayer acquired from budding through the endoplasmic reticulum (ER). The phospholipid content of the ER membrane differs from that of the plasma membrane (PM). The phospholipase A2 (PLA2) superfamily consists of a large number of members that specifically catalyze the hydrolysis of phospholipids at a particular position. Here we show that the CM-II isoform of secreted PLA2 obtained from *Naja mossambica mossambica* snake venom (CM-II-sPLA2) possesses potent virucidal (neutralising) activity against HCV, DENV and JEV, with 50% inhibitory concentrations (IC50) of 0.036, 0.31 and 1.34 ng/ ml, respectively. In contrast, the IC50 values of CM-II-sPLA2 against viruses that bud through the PM (Sindbis virus, influenza virus and Sendai virus) or *trans*-Golgi network (TGN) (herpes simplex virus) were >10,000 ng/ml. Moreover, the 50% cytotoxic (CC50) and hemolytic (HC50) concentrations of CM- II-sPLA2 were >10,000 ng/ml, implying that CM-II-sPLA2 did not significantly damage the PM. These results suggest that CM-II-sPLA2 and its derivatives are good candidates for the development of broad- spectrum antiviral drugs that target viral envelope lipid bilayers derived from the ER membrane. Cellular membrane compartments can be categorized into two groups; the first group consists of the endoplasmic reticulum (ER), unclear envelope, lipid droplets and *cis*-Golgi (ER-NE-*cis*-

Golgi lipid territory) and the second group consists of the *trans*-Golgi, plasma membrane (PM) and endosomes (*trans*-Golgi-PM-EE membrane territory) **[12-13]**. The ER-NE-*cis*-Golgi membranes have lipid packing defects, whereas the *trans*-Golgi-PM-EE membranes show tight packing of phospholipids **[14]**. Additionally, the phospholipid contents of the ER-NE-*cis*-Golgi membranes differ from those of the *trans*-Golgi-PM-EE membranes. Enveloped viruses acquire their envelope lipid bilayers from host cellular membranes **[15]**. Consequently, the phospholipid contents of viruses budding through the ER-NE-*cis*-Golgi membranes differ from those of viruses budding through the *trans*-Golgi-PM-EE membranes **[15-16]**.

IV. Phospholipase A2 Isolated from the Venom of Crotalus durissusterrificus Inactivates Dengue virus and Other Enveloped Viruses by Disrupting the Viral Envelope

The Flaviviridae family includes several virus pathogens associated with human diseases worldwide. Within this family, Dengue virus is the most serious threat to public health, especially intropical and subtropical regions of the world. Currently, there are no vaccines or specific antiviral drugs against Dengue virus or against most of the viruses of this family. Therefore, the development of vaccines and the discovery of therapeutic compounds against the medically most important flaviviruses remain a global public health priority.We previously showed that phospholipaseA2 isolated from the venom of Crotalus durissus terrificus was able to inhibit Dengue virus and Yellow fever virus infection in Vero cells. Here, we present evidence that phospholipase A2 has a direct effect on Dengue virus particles, inducing a partial exposure of genomic RNA, which strongly suggests inhibition via the cleavage of glycerophospholipids atthevirus lipid bilayer envelope. This cleavage might induce disruption of the lipid bilayer that causes destabilization of the E proteins on the virus surface, resulting in inactivation. We show by computational analysis that phospholipaseA2 might gain access to the Dengue virus lipid bilayer through the pores found one achofthetwenty3-foldvertices of the E protein shell on the virus surface. In addition, phospholipase A2 is able to inactivate other enveloped viruses, highlighting its potential as an atural product lead for developing broad-spectrum antiviral drugs.

The Flaviviridae family includes several virus pathogens associated with human diseases worldwide. Clinical conditions can vary from febrile or hemorrhagic diseases for Dengue virus (DENV) and Yellow fever virus (YFV), encephalitis for Saint Louis encephalitis virus (SLEV), Japanese encephalitis virus (JEV), Tick-borne encephalitis virus (TBEV), West Nile virus (WNV), and Rocio virus (ROCV) to hepatitis for Human hepatitis virus (HCV) and Human Pegivirus (HPgV). Currently, preventative vaccines for humans are available only for YFV,TBEV, and JEV and specific antiviral treatment only for HCV **[17]** .Therefore, the development of vaccines and the discovery of therapeutic compounds against the medically most important flaviviruses remain a global public health priority **[18]**. Of the diseases caused by viruses of the Flaviviridae family, dengue is a major threat to public health. It is estimated that 390 million dengue infections occur per year, with 100 million manifesting some type of symptoms **[19]** and approximately two million requiring hospitalization **[20–22]**. The major goal of anti DENV therapy is to prevent patients from developing the severe forms of the disease **[23]**. Members of the Flaviviridae family include viruses with a positive-sense, single-stranded RNA genome of approximately 11,000 nucleotides, surrounded by a nucleocapsid and covered by a lipid envelope in which viral glycoproteins are anchored. The RNA genome encodes a single poly-protein that is proteolytically cleaved in to three structural proteins (C-prM/M-E) and seven non-structural proteins (NS1-NS2A-NS2B-NS3-NS4A-NS4B- NS5) **[24]**. Natural products of ferahuge amount of compounds with a great diversity of chemical structures, the result of biosynthetic processes that have been modulated over millennia through evolution. Natural products have served as important sources of drugs for medical purposes. Tubocurarine, a toxical kaloid with skeletal muscle relaxant properties and obtained from the bark of the South American plant Chondroden drontomen to sum, was the first naturally occurring toxin used in medicine **[25]**. Since 1970, more than40drugsderivedfromnatural products have been approved for use in humans **[26–28]**. Among natural products, venoms are complex mixtures of many different components, such as metalloproteinases, serine proteinases, potassium channel binding neurotoxins, proteolytic enzymes, cytotoxins, pre and post-synaptic neurotoxins, cardiotoxins, and phospholipaseA2s, which can provide clues for designing the rapeutically useful molecules **[29]**. Indeed, Ferreira et al. **[30]** provided a good example of the potential of snake venom components for successful drug development. These authors identified brady kinin-potentiating peptides from the Brazilia narrow head viper (Bothrops jararaca) venom that were used to develop an inhibitor(captopril) of the angiotensin-converting enzyme that is widely used as an anti-hypertensive agent **[31]**. Two other drugs, Tirofiban and Eptifibatide, were designed based on snake venom components and are available in the market

as antiplatelet agents **[32, 33]**. In addition, snake venoms and their components have shown antiviral activity against Measles virus **[34]**, Sendai virus **[35]**, Dengue virus **[36, 37]**, and Human immunodeficiency virus (HIV) **[38]**. One of the main components of snake venom is secreted phospholipase A2 (sPLA2), which has shown systemic toxicities that include myotoxicity, cardiotoxicity, neurotoxicity, nephrotoxicity, hepatotoxicity, reprotoxicity, and systemic hemorrhage **[39 – 43]**. The sPLA2 isolated from snake venoms and others also shown antiviral activity against HIV **[38, 39,40]**, adenovirus **[41]**, Newcastle virus **[42]**, and Rous virus **[43]**. In addition, we have recently found a high antiviral effect of sPLA2 (crotoxin, a dimeric compound composed of PLA2-CB and crotapotin, isolated PLA2- CB and PLA2-inter-cro) from Crotalus durissus terrificus venom against DENV and YFV **[44]**. In this study, we further analyzed the antiviral effect of PLA2-CB against dengue virus and three other enveloped viruses.

V. Multiple Roles of PhospholipaseA2 during Lung Infection and Inflammation

Inflammation of the lung marked by excessive recruitment of neutrophils from circulation to the air way is a common feature among several pathological lung disorders, particularly those involving infection **[45,46,47,48,49,50]**. Although neutrophils serve a protective role by targeting and eliminating bacterial invaders, excessive neutrophil recruitment and accumulation can cause over activity of the nonspecific neutrophil destructive capabilities, resulting in severe host lung tissue damage **[53]**. Inflammation associated with bacterial pneumonia results from directin fection of the upper air way by either gram-positive pathogens, such as *Streptococcus pneumoniae*, or gram negative species, such as *Pseudomonas aerugi- nosa* **[49]**. *P. aeruginosa* is also the major pathogen colonizing the air way and resulting in neutrophilic lung destruction occurring in the heritable disease cystic fibrosis (CF) **[47]**. Acute respiratory distress syndrome (ARDS) is marked by an influx of inflammatory cells, large consisting of neutrophils, resulting in increased permeability of the capillary/alveolar barrier and severely impairing oxygenation **[48]**. Although ARDS is not necessarily associated with infection by a specific pathogen, it is often a consequence of sepsis and frequently associated with no so comical infections **[48]**. As that causes reversible air-way obstruction involving an aberrantly regulated inflammatory response **[47]**. Eosinophils are the effect or immune cells during the asthmatic process and allergens more so than infectious organisms serve as the trigger for an asthmatic attack **[47]**. Severe asthmatic attacks can be exacerbated by respiratory infections, and the pathological process in these severe attacks involves a significant neutrophil presence **[45]**. Chronic obstructive pulmonary disease (COPD) results in air way obstruction that is not fully reversible and is generally brought on by environmental exposure to pollutants, such as cigarette smoke and asbestos **[52]**. Inflammation and air way remodeling are key features in the progression of COPD **[45]**. Since inflammation is a key common component characterizing the pathology of many clinically distinct lung diseases, understanding the mechanisms governing the inflammatory process in the lung may reveal versa tilter at men options that could have a beneficial impact on multiple lung disorders. It has become increasingly appreciated over the past couple of decades that the enzyme phospholipase A2 (PLA2) is an important factor in lung diseases that involve inflammation **[51]**. The defining enzymatic function of PLA2 is the cleavage of membrane phospholipids into smaller bioactive molecules that can then participate in a plethora of cellular processes. Determining the particular role of PLA2 in the setting of lung inflammation has proven quite challenging, because this enzyme represents a family of over 20 distinct proteins with various structural and biochemical characteristics **[51]**. For the purposes of this review, the PLA2 enzymes are segregated in to six major classes based on biochemical properties: secretary PLA2s (sPLA2s), cytoplasmicPLA2s (cPLA2s), calcium independent PLA2s (iPLA2s), lysosomalPLA2s, platelet- activating factor acetyl hydrolases (PAF-AHs), and PLA2s of bacterial origin (Table1). PLA2 isoforms representing each of these major groups have been reported to contribute to either the promotion or there solution of inflammation occurring in the lung during various disease processes **[51]**. Unifying principle for the role of PLA2s in lung disease remain elusive owing tothenumbersofPLA2 isoforms that are expressed in the lung combined with the multiple and distinct functions attributable to each isoform. These circumstances represent a significant challenge for the design of anti-inflammatory therapeutics based on modulating the PLA2 enzymatic activity. The purposes of this review are to highlight findings of the roles variousPLA2s take part in during lung infection and inflammation and to illustrate the importance of PLA2 in lung disease.

VI. BE-I-PLA2, a Novel Acidic PhospholipaseA2 from Bothrops erythromelas Venom: Isolation, Cloning and Characterization as Potent Anti-Platelet and Inductor of Prostaglandin I2 Release by Endothelial Cells

PhospholipasesA2 (PLA2, EC3.1.1.4) are enzymes that catalyze the hydrolysis of the sn-2 fatty acyl bond of

phospholipids to release free fatty acids and lysophospholipids. These enzymes have been found in mammalian tissues, arthropods and in all snake venoms. Based on their source, amino acid sequence, chain length and disulfide bond patterns, PLA2s are divided in 11 groups. Snake venomPLA2s are divided into groups I and II, and most of the PLA2s from Viperidae venom belong to class II **[54]**. PLA2s from snake venoms display several biological effects, including pre or postsynaptic neurotoxicity **[55, 56],** cardiotoxicity **[57]**, myotoxicity **[58]**, platelet aggregation induction or inhibition **[50,60]** and hypotension **[61]**. Actually, according to their platelet effects, snake venoms PLA2 can be divided in to three groups: class A includes the phospholipases able to induce platelet aggregation; class B: PLA2 enzymes which inhibit platelet aggregation induced by several physiological agonist; class C: PLA2 that presenting biphasic responses on platelets (proandanti-aggregating properties) **[62]**. Platelets and endothelium are important components of the homeostatic mechanism. The endothelium is responsible to maintain blood fluidity by producing inhibitors of aggregation platelet and blood coagulation, by modulating vascular tone and permeability, and by providing aprotective envelope separating hemostatic blood components from reactive sub- endothelial structures. Platelets are responsible by the primary hemostasis, by forming large multicellular aggregates, thus creating a physical barrier that limits blood loss from vessels, and by accelerating coagulation cascade activation and fibrin formation **[63]**. In this paper were ported the purification, cloning and action in platelets and endothelial cells (HUVECs) of the first phospholipaseA2 isolated from Bothrops erythromelas venom, a small Viperidae snake of great epidemiological relevance to Brazilian Northeastern region.

VII. In Vitro Evaluation of Antiviral / Virucidal Activity of Naja Nubiae (Elapidae) Venom Against Rift Valley Fever and Herpes Simplex Virus Type -1 (HSV-1) Using Cell Culture

Viruses are capable of rapidly mutating and infecting host cells, sometimes aided by virus-coded peptides that counteract immune defense of host cells. Although a large amount of compounds for inhibiting multiple viral infections and disease progression have been recognized, the discovery of more efficient agents is urgent. Furthermore, Very few viral vaccines are accessible, and not all are effective, in proportion to the wide variety of viral diseases. Thus, new antiviral substances extracted from natural products, including those extracted from venom animals, have been prospected **[64]**.

Venoms are complicated mixtures of hundreds of molecules, mostly peptides that present a wide range of biological activities and have developed to target the biochemical machinery of various pathogens or host cellular structures. In addition, non-venomous compounds have antiviral activity. Peptides described from animal venoms presenting antiviral activity, strengthening them as significant instruments to develop new virucidal agents. Rift Fever Virus (RVF), Dengue viruses are members of the Bunya viridae family and the genus phlebo-virus; has been separated from sheep and animals in Kenya. By 1944, and was separated from the Sem liki Forest in Uganda. In 1950-1 a large outbreak occurred in South Africa. It reached Egypt in 1979-1980, with an infection of 200,000 or more individuals and 600 fatalities. In addition, in 1979, the disease moved to Madagascar. RVF emerged in Saudi Arabia and Yemen in the 21st century and reported 200 deaths. It came to Sudan in 2007 **[65]**. RVF has economic effects as it then transmits animals to humans, causing fever followed by complications in the eyes. Infection with RVF virus can lead to elevated mortality rates in newborn livestock and adult abortions **[66]**. A few commercially available antiviral drugs can cause serious and significant adverse effects, particularly for patients receiving lifelong therapy for illnesses such as HIV. In addition, viruses have the ability to trick and infect host cells rapidly. All of these facts together have led to the prospecting of new antiviral drugs, particularly from natural products, as they make up more than 25% of the new drug prototypes approved in recent decades **[67]**. Among natural product sources, animal venom has disclosed a huge potential for drug discovery **[68, 69, 70]**, and despite the damaging action mechanism of animal venom, most of them have potential medicinal characteristics to cure illnesses. So, the present work aimed to evaluate the antiviral / virucidal activity of Naja nubiae (Elapidae) venom against RVFV and HSV-1 as an economy impact virus infection on the human.

VIII. Antiviral Activity of Animal Venom Peptides and Related Compounds

Considering the most common pathologies in humans and other animals, cardio-vascular and infectious diseases and cancer are among the leading causes of deaths. The cultural and educational background of affected people largely influences the prevention and treatment of human diseases; nevertheless, the availability of new drugs contributes greatly to mitigating diseases. More than 200 viruses are known to cause human diseases **[71, 72]**. Some of

them present high public health importance, such as cytomegalo-virus (CMV), Epstein-Barr virus (EBV), hepatitis Band C viruses (HBVand HCV, respectively), herpess implex virus(HSV), human immune-deficiency virus(HIV), rabies virus and E bolavirus. The most recent worldwide estimates presented by the World Health Organization (WHO) reported1.5million deaths caused by HIVin2012,400 million people living with hepatitis Bor C, 80% of liver cancer deaths caused by hepatitisviruses,500 thousand cases of cervical cancer caused by HPV infection, and over250 thousand cervical cancer deaths each year **[73]**. The very few antiviral drugs commercially available can induce severe and considerable adverse effects, especially to those patients receiving lifelong treatment for diseases such as HIV. Furthermore, viruses possess rapid mutational capacity to trick and infect host cells. All these facts together have propelled the prospection for new antiviral drugs, particularly from natural products, as they constitute more than25% of then ewdrugproto- types approved in the last decades **[74]**. Among sources of natural products, animal venoms have revealed a great potential for drug discovery **[75–77]**, and despite the harmful action mechanism of animal venoms, most of them have components holding potential medicinal properties to cure diseases. It is widely reported in the literature that animal venoms are rich sources of antimicrobial substances, and contain a vast array of active biological compounds with distinct chemical structures **[78]**.Thus, antimicrobial peptides (AMPs) a diversified group of peptides that exert essential function in the innate immune host response, when invaded by pathogenic organisms, such as bacteria, fungi and virus are considered the first line of defense of many organisms, including plants, insects, bacteria and vertebrates **[79, 80]**.

IX. Crotoxin and phospholipases A2 from Crotalus durissus terrificus showed antiviral activity against dengue and yellow fever viruses

Dengue virus (DENV) and yellow fever virus (YFV), members of the genus Flavivirus, family Flaviviridae, are two of the most important arboviruses in public health **[81]**. Dengue is the most rapidly spreading arbovirus disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries **[82]**. Infection with any of the four DENV serotypes (DENV-1, -2, -3 and -4) can be asymptomatic or can lead to a wide spectrum of disease, in some cases with fatal outcome **[83]**. YFV is the causative agent of severe acute hemorrhagic fever with high mortality. Effective vaccines against yellow fever have been available for almost 70 years and are responsible for a significant reduction of occurrences of the disease worldwide; however, approximately 200,000 cases of yellow fever still occur annually, principally in Africa **[82, 84]**. There is no specific drug therapy for DENV and YFV infections; therefore, the development of antiviral agents to reduce the morbidity and mortality causes by these two viruses is a public health priority **[83]**. Snake venoms are complex mixtures of toxins and enzymes that show different activities on biological systems, such as cytotoxicity, hemorrhage activity, brady kinin releasing activity, thrombin-like activity, hemolysis, cardiovascular and hypotensive effects, tissue necrosis and neurotoxic effects **[86-92]**. The venom of Crotalus durissus terrificus snake, a South American rattle snake, has shown several biological activities, including antiviral including antiviral activity against measles virus **[93, 94]**. This venomis composed by neurotoxins, crotoxin **[95]**, crotamin **[96]**, phospholipaseA2 “inter-cro” (PLA2-IC) **[96]**, gyroxin **[97]** and convulxin **[99]**. The fraction which pathophysiological aspects are better characterized is the crotoxin. It represents 40–60% of the dry weight of venom and it is the main toxic component with neurotoxic effects **[100,106]**. This component presents two different subunits no covalently linked: crotapotin, an acid component with a molecular weight of w9,000Da and the phospholipase A2, a basic component(PLA2-CB) with a molecular weight of 16,400Da **[101,102]** isolated and characterized several isoforms of each subunit of crotoxin in the venom collected from numerous snakes. Crotoxin is, in fact, a mixture of variants deriving from the combination of subunit isoforms. FourcrotapotinandfourPLA2-CB present in venom collected from numerous snakes was purified and some sequenced **[103]**. The crotapotin isoforms consist of three disulfide-linked polypeptide chains (a, b, g), which result from different proteolytic cleavages of a unique precursor procrotapotin that has been identified from its c DNA. Two c DNAs encoding PLA2-CB isoforms have been cloned and their nucleic acid sequences determined **[104]**.

The PLA2-ICwas first observed by **[105]**, but the enzyme was not isolated or characterized. **[106]** subsequently isolated and characterizedthePLA2-IC demonstrating that was an isoform, showing differences in the C-terminal region when compared with PLA2-CB1andPLA2-CB2 (basic chain of crotoxin). The alignment of the PLA2-CB1, PLA2-CB2andPLA2-IC sequences and phylogenetic analysis showed that PLA2- CB2 isoform showed higher homology with the PLA2-IC isoform and, furthermore, this homology

is greater than that observed betweenPLA2-CB1andPLA2-IC and even between PLA2-CB1and PLA2-CB2.The PLA2-CB2was originated from the duplication of the PLA2-CB1 gene **[97]**. **[107]** demonstrated that thecomplexPLA2-CB1/CA present in crotoxin, stable thanPLA2-CB2/CA association, confirming that PLA2-ICisan isoform of PLA2-CB2, make the association with crotapotin but its biological activity present in the venom of C. d. terrificus. In this study, we evaluated the antiviral activity of crude venom and isolated toxins from Crotalus durissus terrificus and found that phospholipasesA2 showed a high antiviral effect against DENV and YFV.

X. Secreted phospholipases A2, a new class of HIV inhibitors that block virus entry into host cells

HIV-1 infection is initiated by the interaction of the virion envelope complex (gp120/gp41) with at least 2 cellular receptors: the CD4 molecule (108, 109 and a member of the chemokine receptor family **[110-113]**. Subsequent to binding with these cellular receptors, the gp120/gp41 complex undergoes conformational changes that mediate fusion of the viral membrane with the target-cell membrane **[114-116]**. After virus-cell fusion, virion disassembly occurs (un-coating) to release the reverse transcription (RT) complex that dissociates from the plasma membrane and moves toward the cell nucleus **[115]**. This complex contains all the viral functions necessary for the synthesis of the proviral DNA, its transport to the cell nucleus, and its integration into the host cell DNA **[116-119]**. The molecular basis of viral tropism has now been well characterized and resides in the ability of gp120 to interact specifically with a chemokine receptor **[110-116]**. Macrophage-tropic (M-tropic) strains of HIV-1 replicate in macrophages and CD4+ T cells and use the CC chemokine receptor CCR5 (R5 viruses). T-cell–tropic (T- tropic) isolates of HIV-1 replicate in primary CD4+ T cells and established CD4+ T cells and use the CXC chemokine receptor CXCR4 (X4 viruses). Usually, R5 viruses have a non–syncytium-inducing (NSI) phenotype, whereas X4 viruses have a syncytium-inducing (SI) phenotype (10). Several HIV-1 inhibitors have been described to block HIV entry into cells by antagonizing the interaction between gp120 and the corresponding chemokine receptor. Such inhibitors have been derived from CC or CXC chemokines **[110,112,122,123]** or are small-molecule inhibitors that bind to the co-receptor **[124,125]**. In addition, recent advances in AIDS research have focused on the development of new combination therapies that have led to a dramatic and sustained reduction of viral load **[126-128]** . Although these therapies extend the life of patients, such approaches require rigorous compliance with complicated and expensive drug regimens that cause significant side effects. These factors, coupled with the emergence of resistant viruses that escape to treatment with time, argue for the continued development of new compounds capable of protecting cells from HIV replication. Secreted phospholipases A2 (sPLA2s; 14 kDa) are found in mammalian tissues and animal venoms and catalyze the hydrolysis of glycerophospholipids to release FFAs and lysophospholipids **[129-134]**. They have been classified into different groups on the basis of the number and position of the cysteine residues present in their sequences **[131,134]**.

These sPLA2s have a similar overall organization and the same catalytic mechanism but display very distinct pharmacological effects **[129,130,134]**. So far, 6 mammalian sPLA2s referred to as group IB, IIA, IIC, IID, V, and X have been cloned and associated with different physiological and pathological processes **[132-136]**. Aside from their function as enzyme, sPLA2s have been shown to associate with specific membrane.

XI. Antiviral activity of Acanth asterplanci phospholipase A2 against human immunodeficiency virus

The crown of thorns starfish *Acanthaster planci*is one of the most dangerous coral predators currently contributing to the degradation and loss of Indonesia's highly diverse reefs, which is a major problem for coral management programs in the Pacific Ocean **[137,138]**. Outbreaks of *A. planci* have occurred at many locations throughout the Indo-Pacific region as a result of anthropogenically elevated nutrient levels and overfishing **[139,140]**. Techniques used to manage these outbreaks include implementing biosecurity measures and managing the environmental conditions that lead to outbreaks and disrupting the starfish spawning success **[140-142].** These management strategies give rise to large quantities of starfish waste; in the present study, we aim to identify ways in which this waste may be utilized **[141-146]**. The glandular tissue around the venomous spines on the body surface of *A. planci* produces toxins. Crude venom (CV) extracted from *A. planci* has a range of biological activities including hemolytic, myonecrotic, capillary permeability-in-creasing, hemorrhagic, edema-forming, mast cell histamine-releasing, phospholipase A2 (PLA2), anticoagulant, and cardiovascular activity, as well as mouse lethality **[147]**. CV comprises several bioactive protein toxins, including plancinin, plancitoxins I and II, and PLA2 enzymes **[142]**. Plancinin acts as a coagulant factor in the human blood coagulation cascade through the activation of prothrombin,

and it significantly inhibits factor X activation through both intrinsic (factor IX a factor VIII a–phospholipids–Ca21) and extrinsic (factor VIIa–tissue factor– phospholipids–Ca21) mechanisms **[148]**. Plancitoxins have potent hepatotoxicity, similar to that of mam Malian deoxyribo nuclease II, which results in deoxyribonucleic acid (DNA) degradation during apoptosis and engulfment-mediated DNA degradation **[147]**. *A. planci* phospholipases A2 (AP-PLA2-I and -II) have hemolytic activity only in the presence of phosphatidyl choline (PC), which releases fatty acids that act as antibacterial agents and also possess myotoxic activity **[146,149]**. PLA2 can be extracted from the venomous spines of *A. planci* [**142,146]**. In a previous study, PLA2 was purified from *A. planci* using a rapid and efficient method, which produced a single band of PLA2 protein with specific activity 3-20 times stronger than that of CV **[150,151]**. PLA2 from snake venom exhibits antiviral activity against human immunodeficiency virus (HIV); it interacts with host cells and prevents the intracellular release of virus capsid proteins, thereby blocking viral entry into the cells before virion un-coating **[152,153]**. PLA2 from bee venom has been shown to block the replication of both M- and T-tropic HIV virions by behaving as a ligand for the HIV-1 co-receptor CXCR4 **[152,154]**. AP-PLA2 exhibits some of the same characteristics as PLA2 from snake and bee venom, suggesting that AP-PLA2 could potentially have anti-viral activity against HIV. Based on this information, the present study explores the characteristics of AP-PLA2 and assesses its potential as a cheap, natural, safe, and environmentally friendly drug for the treatment of HIV infection.

XII. Therapeutic Potential Of Snake Venom

Annually 2.5 million people are bitten by snakes, more than 100,000 fatally. In India a large no of people suffer and die every year due to snake venom poisoning. Venom has been used in the treatment of a variety of pathophysiological conditions in Ayurveda, homeopathy and folk medicine. Snake venom is a natural biological resource, containing a complex mixture of enzymes, peptides and protein of low molecular weight with specific chemical and biological activities. Majorly it evolved a vast array of peptide toxins for prey capture and defense. These peptides act like an invaluable source of ligands by acting upon a wide variety of pharmacological targets. Snake venom contains several neurotoxic, cardiotoxic, cytotoxic, nerve growth factor, lectins, haemorrhagins, disintigrins, and many other different enzymes. These proteins not only responsible for death to humans and animals, but can also be used for the treatment of thrombosis, cancer, HIV, arthritis, against microbes, anti-viral and many other diseases. With the advent of biotechnology, the efficacy of such treatments has been substantiated by purifying components of venom and delineating their therapeutic properties. This review will focus on certain snake venom components and their applications in health and disease.

Paracelsus, the 15th century philosopher, had said – “In all things there is poison; there is nothing without poison. It only depends upon the doses, whether a poison is a poison or not”. We now understand that in many cases it is the dose that differentiates a poison from a remedy, which means that any chemical can be toxic if the dose is high, and this is also the basis of modern toxicology. Paracelsus also said that a poison can counteract another and this is the foundation of chemotherapy, antibiotics and immune prevention. It is now well accepted that a poisonous substance could be used as a drug by proper administration, while a life-saving drug might become a poison with indiscriminate use. Many active secretions produced by animals have been employed in the development of new drugs to treat diseases such as hypertension and cancer. Snake bite injuries and deaths are socio-medical problems of considerable magnitude. In India a large number of people suffer and die every year due to snake venom poisoning. Snake venom, though greatly feared, is a natural biological resource, containing several components that could be of potential therapeutic value. Snake venom toxins contributed significantly to the treatment of many medical conditions. There are many published studies describing and elucidating the therapeutic potentials of snake venom. Snake venoms are the secretion of venomous snakes, which are synthesized and stored in specific areas of their body i.e. venom glands. Most of the venoms are complex mixture of a number of proteins, peptides, enzymes, toxins and non-protein inclusions **[155]** . Many of them are harmless, but some can produce toxicity at certain degree. Snake venoms cause significant mortality and morbidity worldwide, and strike fear in most of us.

XIII. CoaTx-II, a new dimericLys 49 phospholipase A2 from Crotalusoreg anusabyssus snake venom with bactericidal potential: Insights into its structure and biological roles

Snake venoms are rich and intriguing sources of biologically active molecules that act on target cells, modulating a diversity of physiological functions and presenting promising pharmacological applications. Lys49phospholipas2 is one of the multifunctional proteins present in these complex secretions and, although catalytically inactive, has a variety of biological activities, including cytotoxic, antibacterial, inflammatory, antifungal

activities. Herein, a Lys 49 phospholipaseA2, denominated Coa Tx-II from Crotalus oreganus abyssus, was purified and structurally and pharmacologically characterized. Coa Tx II was isolated with a high degree of purity by a combination of two chromatographic steps;

Molecular exclusion and reversed phase high performance liquid chromatography. This toxin is dimeric with a mass of13868.2Da (monomeric form), as determined by mass spectrometry. CoTx II is rich in A rg and Lys residues and displays high identity with other Lys49PLA2 homologues, which have high isoelectric points. The structural model of dimeric CoaTx-II shows that the toxin is non-covalently stabilized. Despite its enzymatic inactivity, in vivo CoaTx-II caused local muscular damage, characterized by increased plasma creatine kinase and confirmed by histological alterations, in addition to anti-inflammatory activity, as demonstrated by mice pawed main duction and proinflammatorycytokineIL-6 elevation. CoaTx-II also presents antibacterial activity against gram negative (Pseudomonas aeruginosa 31NM, Escherichia coli ATCC25922) and positive (Staphyloccocus aureus BEC9393 and Rib1) bacteria. Therefore, data show that this newly purified toxin plays a central role in mediating the degenerative events associated with envenomation, in addition to demonstrating antibacterial properties, with potential for use in the development of strategies for anti-venom therapy and combating antibiotic-resistant bacteria.

XIV. Mechanisms of virus resistance and antiviral activity of snake venoms

Viruses depend on cell metabolism for their own propagation. The need to foster an intimate relationship with the host has resulted in the development of various strategies designed to help virus escape from the defense mechanisms present in the host. Over millions of years, the unremitting battle between pathogens and their hosts has led to changes in evolution of the immune system. Snake venoms are biological resources that have antiviral activity, hence substances of significant pharmacological value. The biodiversity in Brazil with respect to snakes is one of the richest on the planet; nevertheless, studies on the antiviral activity of venom from Brazilian snakes are scarce. The antiviral properties of snake venom appear as new promising therapeutic alternative against the defense mechanisms developed by viruses. In the current study, scientific papers published in recent years on the antiviral activity of venom from various species of snakes were reviewed. The objective of this review is to discuss the mechanisms of resistance developed by viruses and the components of snake venoms that present antiviral activity, particularly, enzymes, amino acids, peptides and proteins.

XV. A Phospholipase A2 With Anticoagulant Activity II Inhibition of the Phospholipid Activity in Coagulation

An anticoagulant factor with phospholipase A2 activity has been isolated from Vipera berus venom. Phospholipase activity was studied on platelet phospholipid and on brain cephalin. The venom factor showed a potent anticoagulant activity: 1 mug impaired the clotting of 1 ml of citrated recalcified platelet-poor plasma. The anticoagulant inhibited clotting by antagonism to phospholipid. The antagonism constant (K an = 6.8-10(-9) M) demonstrated the high affinity of the inhibitor for phospholipid. As with other phospholipases A2, the venom factor was thermo-resistant but very sensitive to photo-oxidation. Both activities (anticoagulant activity and phospholipase activity) were not markedly dissociated by either denaturation or neutralization processes. Slightly different curves of photo-oxidative inactivation of both activities suggested the presence, on the molecule, of two very close sites responsible for phospholipase and anticoagulant activities. The inhibitor effect on coagulation was independent of the hydrolysis process. In fact, lyso-derivatives and fatty acids, resulting from complete hydrolysis with the venom factor, were as active as the native phospholipids. Moreover phospholipase A2 from other viperidae venom, which did not have anticoagulant activity, produced similarly active lyso-derivatives. This showed that the cleavage of the beta-acyl bond does not interfere with the activity of phospholipid. A possible mechanism of clotting inhibition by the venom factor was proposed. Owing to its high affinity for phospholipid, the inhibitor would complex phospholipid at its protein binding site impairing the normal arrangement of coagulation protein factors and, consequently, their activation. The positive charges of the inhibitor (pI = 9.2) could bind with phosphoryl or carboxyl groups of phospholipid, making them unavailable for protein binding. The complex formation involves a loss of dissociating capacity of the enzyme towards its substrate. This required an additional interaction of the inhibitor with a coagulation protein factor. The inhibitor could be removed from the complex by specific antibodies, permitting recovery of normal phospholipid-protein interaction. The role of calcium in the complex has not yet been elucidated. This venom factor affords a useful tool for investigating the phospholipid-clotting protein interaction **[156]**.

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