The Protein Journal (2021) 40:799–841
https://doi.org/10.1007/s10930-021-10019-4

Bioactive Molecules Derived from Snake Venoms with Therapeutic Potential for the Treatment of Thrombo-Cardiovascular Disorders Associated with COVID-19

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Accepted: 24 August 2021 / Published online: 9 September 2021

Abstract
As expected, several new variants of Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) emerged and have been detected around the world throughout this Coronavirus Disease of 2019 (COVID-19) pandemic. Currently, there is no specific developed drug against COVID-19 and the challenge of developing effective antiviral strategies based on natural agents with different mechanisms of action becomes an urgent need and requires identification of genetic differences among variants. Such data is used to improve therapeutics to combat SARS-CoV-2 variants. Nature is known to offer many biotherapeutics from animal venoms, algae and plant that have been historically used in traditional medicine. Among these bioresources, snake venom displays many bioactivities of interest such as antiviral, antiplatelet, antithrombotic, anti-inflammatory, antimicrobial and antitumoral. COVID-19 is a viral respiratory sickness due to SARS-CoV-2 which induces thrombotic disorders due to cytokine storm, platelet hyperactivation and endothelial dysfunction. This review aims to: (1) present an overview on the infection, the developed thrombo-inflammatory responses and mechanisms of induced thrombosis of COVID-19 compared to other similar pathogenesis; (2) underline the role of natural compounds such as anticoagulant, antiplatelet and thrombolytic agents; (3) investigate the management of coagulopathy related to COVID-19 and provide insight on therapeutic such as venom compounds. We also summarize the updated advances on antiviral proteins and peptides derived from snake venoms that could weaken coagulopathy characterizing COVID-19.

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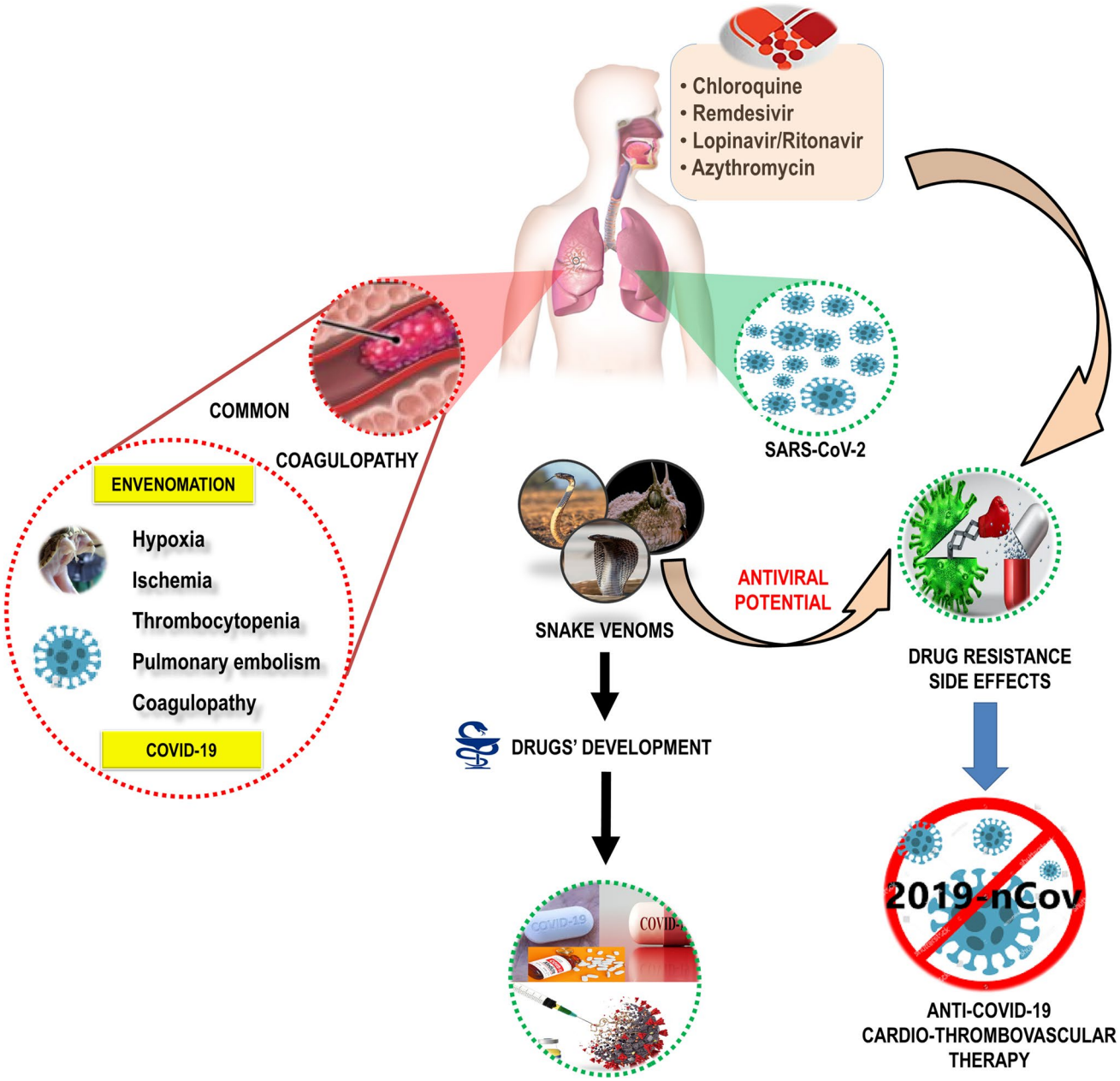
Graphic Abstract



Keywords SARS-CoV-2 variants · COVID-19 · Snake venoms · Coagulopathy · Antiplatelet peptides · Antithrombotic compounds

Abbreviations

ACE-2	Angiotensin Converting Enzyme-2
ACE-2R	ACE-2 receptor
ACh Esterases	Acetyl choline esterases.
ADAMTS13	A disintegrin and metalloprotease with thrombospondin type 1 repeats-13.
Ang	Angiotensin
aPTT	The activated partial thromboplastin time.
ARDS	Acute Respiratory Distress Syndrome
BBPs	Bradykinin Blocker Peptides
BPTI	Inhibitors of bovine pancreatic trypsin
COVID-19	CoronaVirus Disease of 2019
CRISPs	Cysteine-Rich Secretory Proteins

CRP	C-reactive protein
CXCL4	Platelet factor 4
CXCL7	Peptide-2 activating neutrophils
DD	D-Dimers.
DENV	The dengue virus
DIC	Disseminated intravascular coagulation.
DVT	Deep vein thrombosis
E	Envelope
EC	Endothelial cells.
ECs	Endothelial cells
eNOS	Endothelial Nitric Oxide Synthase
FIB	Fibrinopeptide.
G-CSF	Granulocyte colony-stimulating factor
HCoV	Human CoronaVirus
HK	High molecular weight kininogen
INR	The standardized international report
IP-10	The human interferon-inducible protein 10.
KHPM	Prekallikrein, complexed with high molecular weight kininogen
KKS	Kinin-Kallikrein System
LAAO	L-Amino acid oxidases
LMWH	Low molecular weight heparins
MCP-1	Chemoattractant Protein-1 monocyte
MERS-CoV	"Middle East Respiratory Syndrome
MIP	Macrophage Inflammatory Proteins
NETs	Extracellular neutrophils traps
NGF	Nerve Growth Factor
NO	Nitric Oxide
ORF	Open reading frame
PAI-1	The plasminogen activator inhibitor.
PAR	Receptors activated by proteinases
PE	Pulmonary embolism.
PL	Phospholipids
PLA2	Phospholipases A2
PMN	Polymorphonuclear cell
PPK	Plasma prekallikrein
PT	Prothrombin time
PTT	Thrombotic thrombocytopenic purpura
QT	Quick time.
S1 / S2	Subunits 1 and 2
SARS-CoV-2	Severe Acute Respiratory Syndrome-CoronaVirus-2
SV-LAAOs	Snake Venom L-Amino Acid Oxidases
SVMPs	Snake Venom Metalloproteinases
SV-PLA2s	Snake Venom Phospholipases A2
SVSPs	Snake Venom Serine proteinases
TF	Tissue factor.
TLR	Toll-like receptors
TMPRSS2	Transmembrane protease, serine 2
TT	Thrombin time.
VEGF	Vascular Endothelial Growth Factor
VWF	Von Willebrand factor
WHO	World Health Organization.
YFV	Yellow Fever Virus

1 Introduction

Since the beginning of 2020 to the present day, the COVID-19 has been spreading in all the countries throughout the world. Besides the various vaccines being offered to prevent this pandemic there is still no alternative treatment such as drugs that could alleviate the pathophysiological complications caused by SARS-CoV-2. For this purpose, the use of natural sources including snake venoms and their pharmacological components could help identify a treatment for COVID-19. There are no efficient and specific therapies to treat the COVID-19, even if a number of therapeutic approaches have been proposed to combat this pandemic [1–3]. The used repurposed drugs such as chloroquine and remdesivir are able to attenuate some symptoms of this infection. Both have shown efficiency to attenuate some symptoms of COVID-19. Some reports of preclinical trials revealed that the antiplatelet activity of hydroxychloroquine can cause the production of thromboxane A2 and lead to a decrease in fibrinogen levels through its interaction with the arachidonic acid (AA) pathway [3]. Remdesivir, a RNA polymerase inhibitor of SARS-CoV-2, is a nucleoside analog that targets viral replication enzymes during viral replication which results in deadly mutations [4]. Remdesivir has good efficacy against a broad-spectrum of viruses (SARS-CoV, MERS-CoV and SARS-CoV-2) and reduces the time to recovery of hospitalized patients who require supplemental oxygen. Remdesivir may have a positive impact on mortality outcomes while having a favorable safety profile [5]. Although this is an important milestone in the fight against COVID-19, approval of this drug will not be sufficient to solve the public health issues caused by the ongoing pandemic. Further scientific efforts are needed to evaluate the full potential of nucleoside analogs as treatment or prophylaxis of viral respiratory infections and to develop effective antivirals that are orally bioavailable [5].

While it is not unusual for infections to raise the risk of clotting, an unprecedented range of clotting-related disorders have been observed in patients infected with SARS-CoV-2 [6].

From benign skin lesions on the feet to life-threatening thrombotic events, infection by SARS-CoV-2 leads to high prevalence of deadly blood clots [7]. Searching for natural and safe therapeutics that restrain platelet functions and inhibit risk-free plasma factors would be an interesting goal to identify new therapeutic approaches (Fig. 1). For adequate and therapeutic management of COVID-19 coagulopathy, it would be of interest to resort towards natural molecules without side-effects [8].

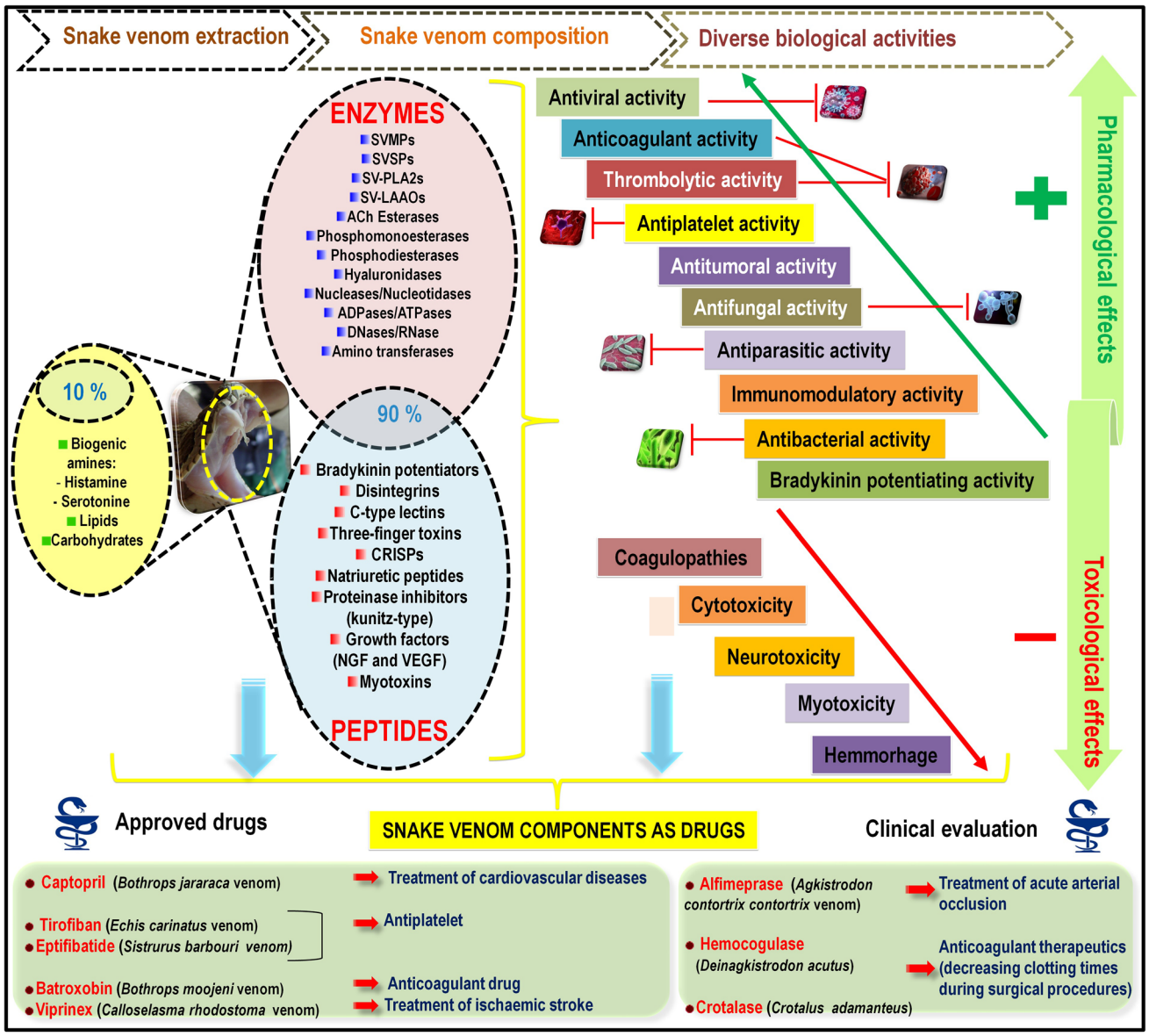


Fig. 1 Snake venom composition, biological activities and snake venom derived-compounds as drugs [11–25] (*ACh Esterases* acetyl choline esterases, *SVMPs* snake venom metalloproteinases, *SVSPs* Snake Venom Serine proteinases, *SV-PLA2s* Snake venom phospholipases A2, *SV-LAAOs* snake venom L-amino acid oxidases, *CRISPs* cysteine-rich secretory proteins, *NGF* nerve growth factor, *VEGF* vascular endothelial growth factor)

Natural components isolated from snake venoms could be a promising alternative given their beneficial pharmacology. Thus, this current review aims to: i) describe some data related to coagulopathies of COVID-19 and snakebite envenomation; ii) provide proven examples of anti-clotting and/or antiplatelet polypeptides derived from snake venoms as potential safe candidate drugs.

2 Usefulness of Snake Venoms and Their Components in the Management of COVID-19 Pathogenesis

Despite the newly developed vaccines against COVID-19, it is important to find additional solutions to fight against infection with SARS-CoV-2. Snake venoms and their components could be a promising alternative given their variety. These components remain highly relevant for use as experimental tools to elucidate several physiological

mechanisms given their selective modes of action. In addition, snake venom derived-compounds can serve as good drugs for developing new biotherapeutics and diagnostics with relevant biomedical applications for many human diseases. Such isolated snake venoms-derived compounds have long been known to possess medicinal and pharmacological properties [9]. Many of them could be used as antithrombotic [10], antiplatelet [11], antibacterial [12], antifungal [13], antiparasitic [14], anti-inflammatory drugs, and interestingly, as potential antiviral against several viral diseases (Fig. 1). Some of these therapeutic applications inherent to compounds derived from snake venoms will be described throughout this review; a particular attention will be given to antithrombotic compounds in relation to SARS-CoV-2 coagulopathy.

With regards to COVID-19 pandemic, some primary care physicians reported that the pathogenesis of COVID-19 brought about by SARS-CoV-2 is initiated by a high hypoxemia in vasculatures and leads to ARDS (Acute Respiratory Distress Syndrome). Collapsed lungs due to many blocked veins by micro-embolism are believed to be the final cause of death for many infected individuals [26].

Coagulopathy corresponds to various disorders causing either hemorrhages or excess coagulation responsible for the formation of clots in the arteries [27]. These disorders can be serious in the case of a simple slowdown in coagulation [28]. Weak hemorrhages may occur spontaneously revealing more serious disorders which may lead to massive bleeding depending on the site and the extent of the bleeding [29, 30]. The hemostatic disorders could be related either to the structural or functional abnormalities of coagulation factors themselves, or either to their deficiencies [21, 31, 32]. The excess of coagulation causing thrombosis is reported after snakebites and also for COVID-19 due to increased concentration of coagulation factors or hyperactivation of platelets. A disturbance of hemostasis on endothelial cells, platelet functions and on various plasma and tissue factors results in an imbalance between their activation and inactivation.

Several molecules from various animal sources, in particular from snake (*Viperidae* and *Crotalidae*) venoms are known to substitute the plasma factors or to interact on the platelet function thus making a possible correction of coagulopathy.

3 SARS-CoV-2 and its New Variants: Infection and Transmission

3.1 β-Coronaviruses and SARS-CoV-2 Outbreak

SARS-CoV-2, similar to other beta-Coronaviruses, is a causative pathogen of a severely contagious infection that can be quickly transmitted via various modes such as through the ingestion of virus loaded-droplets or their direct inhalation through sneezes and coughs. Viral infection also can be spread by spontaneous touch upon contact with contaminated surfaces (https://www.who.int/health-topics/coronavirus#tab=tab_3) [33, 34].

During the decade of 2002–2012, SARS-CoV and MERS-CoV (Middle-East respiratory syndrome coronavirus) were the two earlier coronaviruses to appear in Asia where they spread and caused fatal pneumonia associated with thromboembolic abnormalities in severely affected patients [35–37] (Fig. 2A):

- Guangdong (province of China) was in 2002, the first city of contamination emerged by SARS-CoV where a cluster was formed leading to the infection of 8,098 people and causing around 774 victims in the world through human air routes [35, 36].
- The second coronavirus; MERS-CoV was discovered for the first time in the region of the Arabian Peninsula which was the origin of its strong and rapid spread to other countries (27) where it maintains its high virulence and is considered to be a general real medical condition since 2012. In fact, infected cases with MERS-CoV with ~ 2,494 individuals of which 858 have died [37].
- SARS-CoV-2 was identified in December 2019 where it was found in the Chinese city of Wuhan [38, 39]. Zhu and collaborators have isolated the virus and sequenced it entire genomic RNA in January 2020 [40].

The pandemic of COVID-19 resulting from SARS-CoV-2 infection was characterized by an ongoing outbreak of severe pneumonia accompanied with serious coagulopathy [38, 39]. On January 30th, 2020, the World Health Organization (WHO) has recognized this infectious and deadly disease as a global medical emergency. WHO reported on August 2, 2021 198,022,041 positive infected people and 4,223,460 from whom have died (https://covid19.who.int/) [41]. Further, speeding up of the rate of new cases is more prominent in the European region. Globally, a substantial rise in deaths was likewise accounted with the Delta variant [42].

In Algeria, COVID-19 pandemic has negatively impacted all sectors. According to updated daily reports published by WHO recorded 171 392 confirmed cases of infection including 4 254 deaths on August 2nd, 2021 (https://www.who.int/countries/dza/) [41].

3.2 SARS-CoV-2 Structure, Replication Cycle and ACE-2 Down Regulation

As one of the seven β-Coronaviruses, SARS-CoV-2 consists of a single-stranded RNA virus comprised of ~ 30 kb nucleotides encoding for its proteome including various catalytically active proteins which exhibit crucial roles at

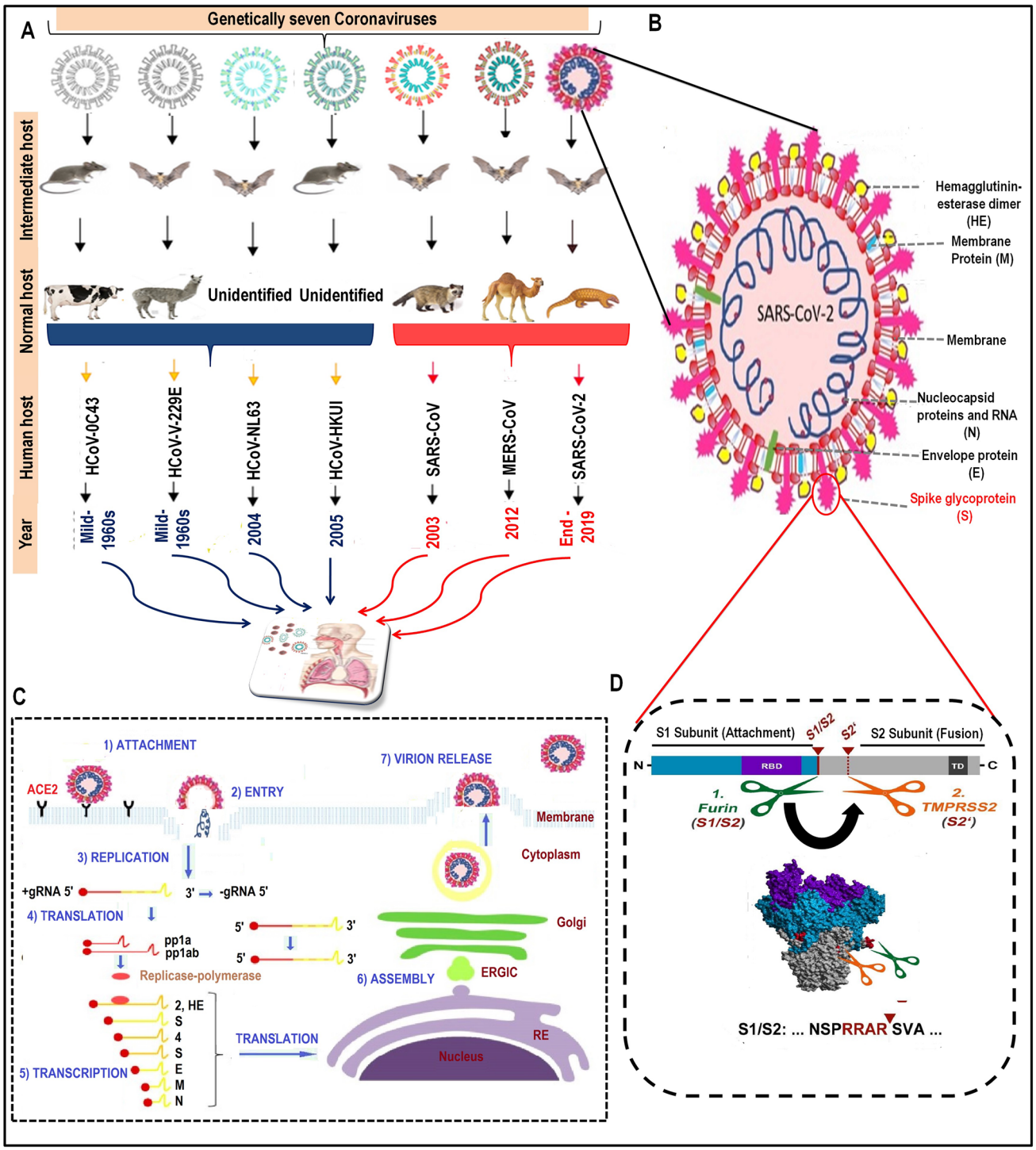


Fig. 2 Overview on coronaviruses outbreak. **A** Origin and transmission of genetically pathogenic HCoVs. **B** Schematic structure of SARS-CoV-2. **C** SARS-CoV-2 replicative cycle. **D** The structure organization and cleavage of Spike protein into domains S1 and S2 for COVID-19 [35, 36, 38, 39, 49]

many stages of viral infection (Fig. 2B). SARS-CoV-2 interacts with the receptor of the angiotensin converting enzyme (ACE-2) receptor in order to internalize into host-cells particularly in the pulmonary alveoli and the vascular endothelium, which both richly express this receptor [43]. Additionally, ACE is a zinc metalloproteinase found in many

other types of cells and tissues including heart, liver, kidneys, testicles and digestive organs [44]. SARS-CoV-2 infection, particularly in ARDS arrays, seems to be significantly correlated to numerous events of hemostatic disorders.

Many groups of researchers reported that SARS-CoV and SARS-CoV-2 shared close sequence similarities [38, 45, 46]. Nonetheless, according to Wang and collaborators [47], the zoonotic transmission of SARS-CoV is mediated by two normal hosts (palm civets and racoon dogs) [47]. SARS-CoV, MERS-CoV and SARS-CoV-2 are the highest virulent β-coronaviruses whilst HCoV-HKU1, HCoV-OC43, HCoV-229E and HCoV-NL63 are pathogens characterized by a low-pathogenicity but remain endemic in individuals (Fig. 2A and 2B) [48]. From today, there are several efforts to develop vaccine formulations to combat COVID-19; some of them are used.

SARS-CoV-2 expresses four structural proteins Spike (S) protein, Membrane (M) protein, Envelope (E) protein and Nucleocapsid (N) protein that are altogether closely implicated in keeping up enhanced viral infection destructiveness. Therefore, they play a crucial role for maintaining enhanced virus virulence. The role of each protein of SARS-CoV-2 during virus replicative cycle is illustrated in Fig. 2B and 2C.

The Spike protein is the main structural protein that stretches along the surface of the virus [49]. Spike protein exhibits double roles during the cycle of SARS-CoV-2 replication: *i)* the virus attachment to ACE-2 receptor on the host cell, and in *ii)* the viral entry into the host cell by prompting the fusion between their respective membranes.

The full 3-dimensional structure of the S-protein was elucidated as a glycoprotein made of three indistinguishable chains (1273 amino acid residues) and including two domains named S1 and S2 subunits [50] (Fig. 2D). The S1 and S2 subunits allow S-protein to bind to ACE-2 receptor and facilitate fusion viral and host cell membranes respectively [40].

The M-protein is responsible for the assembly of SARS-CoV-2 whilst the N-protein covers the viral genomic RNA and assumes its replication and transcription. The binding of N-protein to genomic RNA virions through its N-terminal domain processes the replication and translation of SARS-CoV-2 [51]. Currently, a few studies in progress are focusing on this phase of the SARS-CoV-2 replication cycle to develop effective drugs that could successfully prevent contact between the RNA strand of SARS-CoV-2 and the N-terminal of the N-protein [52].

Several reports revealed that E-protein which is known to be responsible for the virions' assembly, presents other roles in infection since it is involved in stress response of the host cell [53, 54].

During the process of infection, SARS-COV-2 downregulates ACE-2 as it attaches to ACE-2 receptor (ACE-2R) [55]. The transmembrane protease serine-2 (TMPRSS2) is responsible for mediating virus entry through in COVID-19 sickness [40]. The involvement of kinin-kallikrein system (KKS) during COVID-19 disease is evidenced by Cathepsin L which upgrades KKS and regulates bradykinin concentrations. These events may be, in part, promising for possible therapies of this pathogenesis [56].

The Acute Respiratory Distress Syndrome (ARDS) is initiated through the down regulation of ACE-2 expression once SARS-COV-2 attaches to ACE-2R. Subsequently, ARDS was induced by an increase of angiotensin II (Ang II) correlated at the same time to angiotensin 1–7 decrease [57]. It has been reported that induced ARDS by SARS-CoV-2 may be prevented when angiotensin 1–7 effects are enhanced [58]. In addition, both endothelial nitric oxide synthase (eNOS) suppression and the decrease of nitric oxide (NO) are associated with COVID-19 sickness and both events enhance endothelial dysfunction, that prompts thrombotic events and organ failure [59, 60]. Thrombotic events related to endothelial dysfunction are fully discussed in following section.

3.3 New SARS-CoV-2 Variants

At the end of 2020, some countries including United Kingdom (UK), United States (USA), South Africa, Brazil and India have reported the emergence of multiple variants of SARS-CoV-2. Identified variants showed one or more mutations that have undergone in the genomic RNA of the wild-type virus that differentiate them from each other:

- **B.1.1.7**: This variant first detected in the US at the end of December 2020. Genetic investigations revealed that this variant carries at least seven mutations (69/70 deletion, 144Y deletion, N501Y, A570D, D614G, P681H) [61]. This variant was emerged in UK in January 2021 where it caused increased risk of death compared with other variants.
- **B.1.351**: A new variant of SARS-CoV-2 known as B.1.351 emerged in South Africa. The first detected cases of B.1.351 were reported in the US at the end of January 2021. According to (https://www.niid.go.jp/niid/en/2019-ncov-e/10108-covid19-33-en.htmlexternal icon) [62], the Moderna mRNA-1273 vaccine currently used in the US may be less effective against B.1.351 but this speculation needs more scientific investigations.
- **P.1**: P.1 is another new variant SARS-CoV-2 that has been identified in Brazil and US at the end of January 2021· The P.1 carries of about seventeen mutations (including K417T, E484K, and N501Y) that target the receptor binding domain of the spike protein [63]. Zhou and collaborators (2021) [64] suggest that these several mutations might disturb the recognition of the

virus by antibodies released after vaccination with the wild-type SARS-CoV-2.

All these variants shared a specific mutation (D614G) in the amino acid sequence of spike protein that gives them the ability to spread more quickly than viruses without the mutation [65].

At the present time, the expert group convened by WHO has recommended using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma, Delta which will be easier and more practical to discussed by non-scientific audiences The variant Delta, also known as B.1.617.2, was earliest documented in India on October 2020. WHO has considered this variant of concerns (VOC) on May 11, 2021. This VOC shows evidence of increased transmission and more severe disease (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/) [66]. The Delta variant can spread more easily and the strain has mutations on the spike protein that make it easier for it to infect human cells. That means people may be more contagious if they contract the virus and more easily spread it to others. It is now the dominant strain in the world.

4 Thromboembolic disorders in severe COVID-19 compared to that induced after snake envenomation

4.1 Coagulopathy in snake envenomation

Snake envenoming is a real health problem and economic burden in many regions around the world. It was recognized by WHO as neglected tropical diseases of priority because they affect people under 30 years old [67, 68]. According to Kasturiratne and collaborators [69], the estimated burden of snake bite is ~ 1.8–2.7 million cases of bitten individuals and 81,410–137,880 deaths occur every year around the world [70, 71].

Snake venoms are very complex when compared to those of spider or scorpion venoms [72]. They are a rich source of a variety of proteins, and peptides endowed with several pharmacological potentials. The beneficial effects of venom derived components are attributed to disulfide bridged peptides. Snake venom composition is an unpredictable complex combination of ~ 50–200 pharmacologically-active proteins and peptides distributed in major and minor groups [21, 22] (Fig. 1). Therefore, the major groups are snake venom serine proteases (SVSPs), snake venom metalloproteinases (SVMPs), secreted phospholipases A_2 (SV-PLA2s), C-type lectins and disintegrins, while the secondary families comprise nucleotidases (Ntases), phosphodiesterases (PDEs), cysteine-rich secretory proteins, L-amino acid oxidases, Kunitz peptides, three-finger peptides (3FTX) and natriuretic peptides [20–23, 25].

Most of snake venom family components may act at several stages on coagulation system which is considered as the main impaired process after snakebite envenoming [9, 73]. These diverse compounds can cause hemorrhage through various manners. They are good agents at *(i)* damaging endothelial cells as well as disturbing their interactions with the basement membrane, *(ii)* upsetting platelet aggregation which is crucial for blood clotting, *(iii)* impairing the blood coagulation cascade by activating blood coagulation or *(iv)* potentially repressing the blood coagulation cascade [74]. These components are also able to cleave fibrinogen and dissolve the already formed blood clots [74]. These effects explain the disturbance of hemostasis as serious consequences of snakebites. These coagulopathy disorders could be compared to those reported in SARS-CoV-2 infection. Furthermore, many reports highlighted the importance of coagulopathies after snake envenomation which is tightly associated with cardiovascular effects and endothelial dysfunction that are similar to those seen in severe COVID-19. Therefore, many same characteristics are found common between snake envenomations and SARS-CoV-2 pandemic that may help to understand the several thromboembolic events.

Snake venoms induced consumption coagulopathy (VICC) is a typical common pathological feature in practically all snake families. VICC, as clinical complications begin to dominate, may increase when combined with a fatal hemorrhage as venoms contain numerous hemorrhagins (SVMPs) [75]. The hemorrhage induced by SVMPs is the consequence of cleavage of capillary basement membranes leading to an increase of the vascular permeability of blood vessels and resulting in blood extravasation (Fig. 3A) [76]. Snake venoms are capable to cause death by hemorrhage when it is intracranial [77]. In envenomed patients, VICC occurred, when several coagulation factors are activated by procoagulant compounds such as SVMPs, SVSPs and thrombin-like enzymes (TLEs), altogether, these components cause the consumption of clotting factors by snake procoagulant compounds [27, 73, 78, 79]. Multiple factor deficiencies including factors II, V, VIII, X and fibrinogen, lead to an incoagulable blood due to hypofibrinogenemia which is one of the markers of VICC [27].

Several snake venoms are mostly known to induce VICC (Table 1). Snake venom derived procoagulant-components contribute to VICC including:

- Activators of FII isolated from Echis carinatus, Pseudonaja textilis, Notechis scutatus venoms [80, 81].
- Activators of FX derived from Daboia russelii, Bothrops atrox, Cerastes cerastes, Bungarus Ophiophagus venoms [10, 82].
- Activators of FV identified from the venoms of Bothrops atrox and Naja naja oxiana [81].

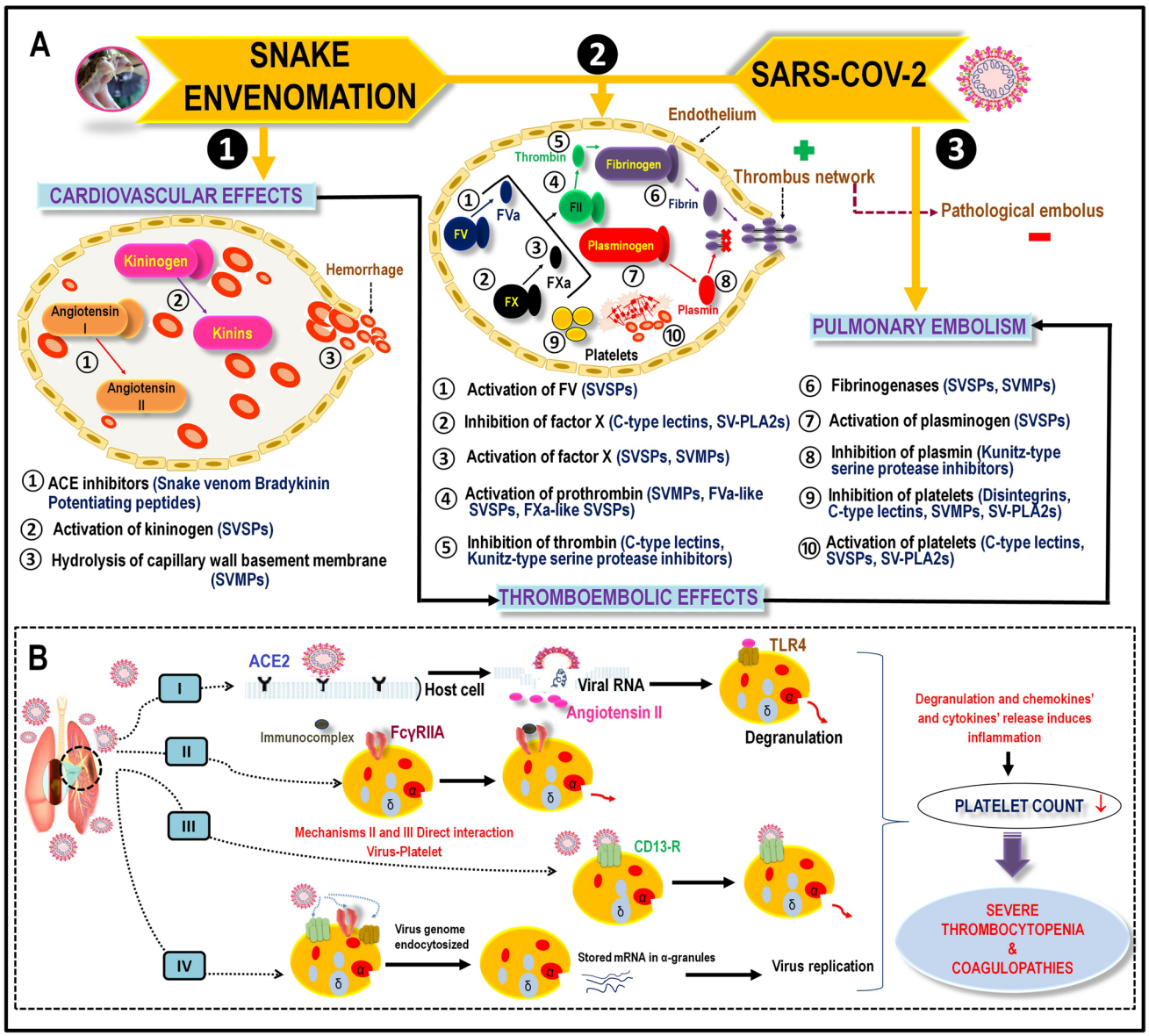


Fig. 3 Cardiovascular and thromboembolic effects induced by snake envenomation and COVID-19 pathogenesis. **A** Synergistic action of several snake venom compounds on cardiovascular and hemostasis systems causing together pulmonary embolism like SARS-CoV-2. **B** Proposed mechanism of interaction between SAR-CoV-2 and platelet receptors. Thrombocytopenia may occur via: **I** SARS-CoV-2/ACE-2R interaction induces the increase in Ang II which in turn interacts with TLR4 and degranulates thrombocytes. **II** SARS-CoV-2 may directly bind to FcγRIIA receptor. **III** The virus binds to CD13 of thrombocytes leading to the secretion of their granulations. **IV** Thrombocyte could serve as a virus production compartment; they make endocytosis of viral genomes and use their stored mRNAs for translation [75, 131–133]

- SVTLEs isolated from Agkistrodon contortrix contortrix venom [83].
- Activators of plasminogen purified from Trimeresurus stejnegeri venom [84]. Some investigations reported that patients experiencing VICC present high levels in some hemostatic parameters such as prolonged prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT), [75, 123, 124]. These parameters (PT, aPTT and INR) are also increased in severe cases of COVID-19.

Procoagulant SVSPs seem to be alone responsible for hemotoxic effects. These procoagulant molecules displayed pharmacological effect by activating a variety of plasma blood clotting factors particularly FII, FV, FVII and FX [30, 125]. Prothrombin activation allows thrombin release,

Table 1 Summary of snakes known to cause venom-induced consumption coagulopathy, the procoagulant toxin, and the factor deficiencies

Procoagulant compounds	Snake species/ Common name	Factor Deficiencies	VICC assay	References
A/Africa				
TLE	*Atheris squamigera* Green bush viper	Fibrinogen	aPTT, fibrinogen	[85]
TLE	*Atheris chlorechis* Western bushviper	Fibrinogen	PT, aPTT, fibrinogen	[86]
TLE	*Atheris nitschei* Great lakes bush viper	Fibrinogen	PT, aPTT, fibrinogen, D-dimer	[87]
TLE	*Cerastes cerastes* Saharan horned viper	Fibrinogen, FV	PT, aPTT, fibrinogen, D-dimer, factor V	[88, 89]
TLE (cerastobin)	*Cerastes vipera* Sahara sand viper	Fibrinogen	PT, aPTT, fibrinogen, D-dimer	[88]
	Proatheris superciliaris Lowland viper	Fibrinogen	PT, aPTT, fibrinogen, D-dimer	[90]
TLE	*Bitis arietans* African puff adders	Fibrinogen	Fibrinogen, PT, clotting factor studies	[91–93]
TLE (Gabonase)	*Bitis gabonica* Gaboon viper	Fibrinogen	Fibrinogen, PT, clotting factor studies	[94]
FII activators	*Echis coloratus* Painted carpet viper	Fibrinogen, ?, FII, FV, FVIII	Fibrinogen, FDP, PT	[95, 96]
FII activators	*Echis ocellatus* West African carpet viper	Fibrinogen, FII, FV, FVIII	fibrinogen, clotting factor studies	[97]
FII activators	*Echis pyramidum* Northeast African carpet viper	Fibrinogen, FII, FV, FVIII	Fibrinogen, PT, clotting factor studies	[98, 99]
SVMP*	*Dispholidus typus* Boomslang	Fibrinogen	PT, aPTT, fibrinogen, FDP	[100]
B/Asia				
FX, FV activators	*Daboia russelii* Russell's viper	Fibrinogen, FV, FX	WBCT20, CT, fibrinogen, clotting factor studies	[101, 102]
FX, FV activators	*Daboia russelii siamensis* Eastern Russell's viper, Siamese Russell's viper	Fibrinogen, FV, FX	PT, non-clotting blood	[103]
TLE	*Hypnale hypnale* Hump-nosed pit vipers	Fibrinogen, FVIII	PT, aPTT, clotting factor studies, D-Dimer	[104]
FII activators	*Echis carinatus* Saw scaled viper	NR	PT	[105]
TLE	*Calloselasma rhodostoma* Malayan pit viper	Fibrinogen	Fibrinogen, FDP, clotting factor studies	[106]
TLE	*Trimeresurus albolabris* White-lipped green pit viper	Fibrinogen	Fibrinogen, FDP, fibrinopeptide A, plasminogen	[107]
TLE	*Trimeresurus macrops*	Fibrinogen	Fibrinogen, FDP, fibrinopeptide A, plasminogen	[108]

Table 1 (continued)

B/Asia				
	Large-eyed pitviper (green pitviper)			
TLE, plasminogen activator	*Trimeresurus stejnegeri*	Fibrinogen	Fibrinogen, FDP, AT-III	[109]
	Bamboo pitviper, Chinese tree viper			
ND	*Rhabdophis subminiatus*	Fibrinogen	PT, aPTT, Fibrinogen, FDP	
	(Red-necked keelback)			
ND	*Rhabdophis tigrinus*	Fibrinogen	PT, aPTT, Fibrinogen, FDP	[110]
	(Tiger keelback			
C/Australia				
FII activators	*Pseudonaja spp.*	Fibrinogen, FII, FV, FVIII	PT, aPTT, Fibrinogen, FDP	[75]
	Brown snake			
FII activators	*Notechis scutatus*	Fibrinogen, FII, FV, FVIII	PT, aPTT, clotting factor studies, D-dimer	
	Tiger snake			
FII activators	*Tropidechis carinatus*	Fibrinogen, FII, FV, FVIII	PT, aPTT, clotting factor studies, D-dimer	
	Rough-scaled snake			
FII activators	*Hoplocephalus spp.*	Fibrinogen, FII, FV, FVIII	PT, aPTT, D-dimer, FDP	
	Broad-headed snakes			
FII activators	*Oxyuranus scutellatus*	Fibrinogen, FII, FV, FVIII	PT, aPTT, clotting factor studies, D-dimer	[111]
	Coastal taipan			
D/Central and South America				
TLE, FX, FV, activators	*Bothrops atrox* (Common Lancehead)	Fibrinogen	PT, aPTT, D-dimer, FDP	[112]
TLE, FII activators	*Bothrops asper* (Lancehead, Terciopelo)	Fibrinogen, FII, FV	PT, aPTT, clotting factor studies, D-dimer	[113]
TLE, FII activators, FX activator	*Bothrops jararaca* (Jararaca)	Fibrinogen, FII, FV, FVIII	Fibrinogen, clotting factor studies	[114]
TLE	*Lachesis* spp. (Bushmasters)	Fibrinogen	Fibrinogen, D-dimer, a2- antiplasmin, FDP	[112]
TLE	*Crotalus durissus* (South American rattlesnake)	Fibrinogen, FII, FV		[114]
E/North America				
TLE	*Crotalus atrox*	Fibrinogen	PT, aPTT, Fibrinogen	[115]
	Western diamondback rattlesnake			
TLE	*Crotalus adamanteus*	Fibrinogen, D-dimer (normal)	PT, aPTT, fibrinogen, D-dimer, FDP, antiplasmin III	[116]
	Eastern diamondback rattlesnake			
TLE	*Crotalus molossus molossus*	Fibrinogen	PT, fibrinogen, FDP	[117]
	Black-tailed rattlesnake			
TLE	*Crotalus horridus*	Fibrinogen	Fibrinogen, FDP	[118]
	Timber rattlesnake			
TLE	*Crotalus helleri*	Fibrinogen	PT, fibrinogen	[119]
	Southern Pacific rattlesnake			

Table 1 (continued)

G/Europe				
FX activator	*Vipera aspis*	Fibrinogen	PT, aPTT, fibrinogen, D-dimer	[120]
	European asp/Asp viper			
ND	*Vipera berus*	Fibrinogen	PT, aPTT, fibrinogen, D-dimer	[121]
	Common European viper)			
ND	*Vipera ammodytes ammodytes*	Fibrinogen	PT, aPTT, fibrinogen, D-dimer	[122]
	Horned viper			

aPTT–activated partial thromboplastin time, CT–clotting time, VCT–venous clotting time, FDP–fibrinogen degradation products, PLA_2–phospholipase A_2, PT– prothrombin time, TLE–thrombin like enzymes, FII–factor II, FV–factor V, FX– factor X, FDP – fibrinogen degradation products; SVMP – snake venom metalloproteinase; NR – not reported

which cleaves fibrinogen, generating polymers of fibrin**.** The formed fibrin possibly becomes pathologic embolus if not dissolved by plasmin and may subsequently disseminate. Thrombin likewise promotes platelet aggregation which together with the fibrin clumps formation, brings about blood clotting [126]. Furthermore, proplatelet SVSPs directly bind to protease activated receptors (PAR-1/PAR-4) on platelet surface and mediate fibrinogen binding to GPIIb/IIIa integrin [127]. The dual roles of SVSPs prompt the quick uptake of important coagulation factors of both extrinsic and intrinsic pathways. These multiple events may ascribe a similarity between thromboembolic abnormalities associated with COVID-19 and those subsequent from snake envenomations. Some SVSPs are good blockers of blood coagulation as either anticoagulant or thrombolytic through different mechanisms of action**:**

I. The anticoagulant SVSPs exhibit their effects by activating the Protein C that in turn inhibits FVa and FVIIIa [128].
II. SVSPs are also potent thrombolytic and are capable for eliminating blood thrombus**;** by acting as SVTLEs or activators of plasminogen that release plasmin cleaves the clots and induces coagulopathy [30, 129].
III. SVSPs can induce depletion of plasma coagulation factors which prevented coagulation and prompted to internal and external bleedings due to non-coagulable blood [30, 129].

Similarly to SARS-CoV-2, thrombocytes are good targets for many compounds isolated from snake venoms such as C-type lectins, disintegrins, SVSPs, and some SVMPs, Ntases and PDEs. Some proteins and peptides induce indirect platelet aggregation through binding to von Willebrand factor (vWF) or collagen and other receptors [73]. Besides, other snake venom components such as SV-PLA2s, disintegrins, C-type lectins, 3FTX are responsible for inhibiting the platelet aggregation, by blocking integrin receptors such as $\alpha_2\beta_3$ [73, 130]. VICC might be enhanced in both situations of activated or prohibited thrombocytes by snake venom compounds resulting in platelets depletion [131, 132]. Clinically, envenomed patients present severe thrombocytopenia which is a main pathogenic complication linked to COVID-19 pandemic. Thromboembolic disorders instigated by snake venoms are frequently accompanied by cardiovascular effects that resemble to infected people with SARS-CoV-2 (Fig. 3A). Several compounds derived from snake venom can induce serious cardiovascular effects marked by a dramatic hypotension observed in envenomed patients.

Snake venom bradykinin potentiating peptides (BPPs) are the main component responsible for vasodilatory effects that can be additionally upgraded by certain multifunctional SVSPs [78]. Snake venoms contain various kallikrein-like SVSPs which contribute to cardiovascular effects due to their kininogenase activity releasing bradykinin from plasma kininogen [133]. At the same time, by degrading the basement membranes of capillaries, SVMPs enhanced hypotension and increased vascular permeability that leads to fall in blood pressure [76]. Snake venom hemotoxic complications including hemostasis unsettling influences and cardiovascular impacts intently take after to coagulopathy related with COVID-19 pandemic.

4.2 Coagulopathy and Thromboembolic Disorders in Severe COVID-19

COVID-19 presents various cardiovascular disorders accompanied with endothelial dysfunction, hypercoagulability and platelet hyperactivation leading to coagulopathy resulting in respiratory distress and pulmonary embolism [6, 134, 135] (Fig. 3 A). Patients presenting cardiovascular illness are vulnerable to risk events associated with COVID-19, while healthy people may develop cardiovascular complications after viral infection [134]. Additionally, indirect effects

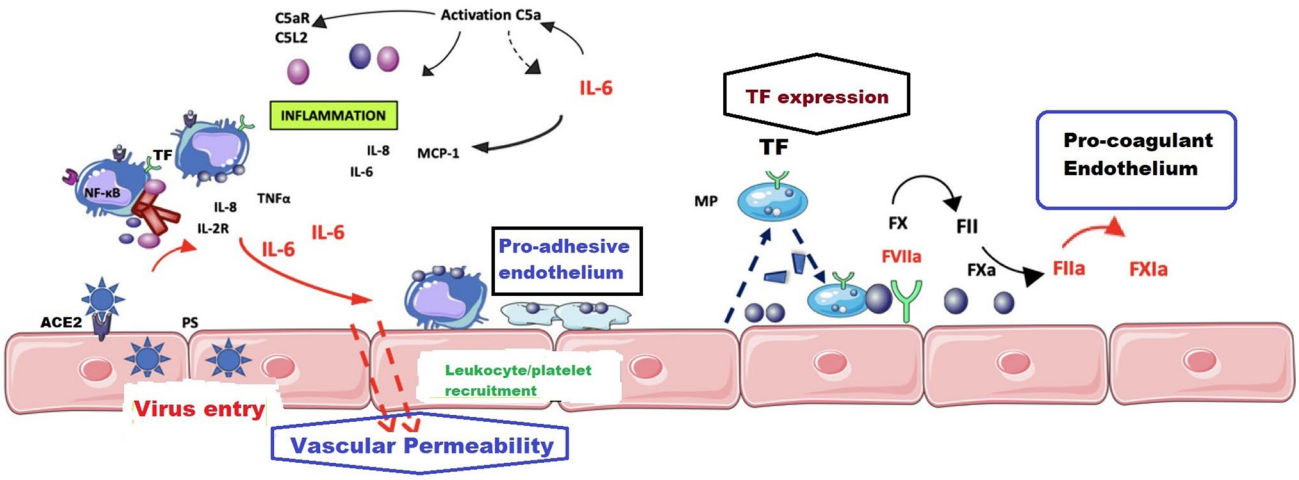


Fig. 4 Interconnection between endothelial cells, inflammatory cells, complement system and the coagulation during the thrombo-inflammatory pathogenesis of COVID-19 [144]. IL-6, partly secreted by monocytes, lymphocytes and endothelial cells in response to infection with SARS-CoV-2, increases vascular permeability, but also the secretion of other pro-inflammatory cytokines (IL-6, IL-8 and MCP-1) by endothelial cells contributing to the cytokine storm. The endothelium thus becomes pro-adhesive. Finally, endotheliitis also participates in the hyper-expression of tissue factor (TF), a major activator of coagulation. (*IL* interleukin, *C* complement, *F* coagulation factor, *MP* microparticles, *PS* phosphatidylserine, *MCP-1* monocyte chemo-attractant protein 1 also called CCL2)

such as hypoxia and hyper inflammatory response increase infection with SARS-CoV-2 and predispose those infected to primarily disseminated intravascular coagulation (DIC) coagulopathy like previous outbreaks of harmful zoonotic coronaviruses [35–37, 136]. Thromboembolic disorders marked by thrombocytopenia highly emerged in COVID-19 pathogenesis particularly in severe case of patients infected by SARS-CoV-2 [137].

Coagulopathy features associated with the outcome of COVID-19 are PT, aPTT, D-dimers, fibrinogen, FDPs and antithrombin III such as in the envenomation cases [138]. Tang and collaborators [138] recommended to follow PT/aPTT, D-dimers and platelet count in diagnosis of COVID-19. COVID-19 sickness revealed a weak delayed aPTT due to the huge increase in Factor VIII and vWF [138].

SARS-CoV-2 infection can, in extreme cases, brings about in cytokine storm correlated to thrombo-inflammation called COVID-19- induced coagulopathy (CIC). CIC would be defined as an immuno-thrombotic response in critically ill patients COVID-19 that is an uncontrolled process [139]. Hemostasis abnormalities associated with COVID-19 such as in the snake envenomation are not hemorrhagic but rather prothrombotic.

Dysfunction of endothelium is considered as a major determinant of microcirculatory impairment by altering the balance of the vascular bed towards more vasoconstriction generating ischemia, inflammation and a procoagulant state. Once SARS-CoV-2 is attached to ACE2 receptor, alteration of endothelial cells (ECs) leads to the release of tissue factor which binds FVII and initiates extrinsic coagulation pathway [140]. Multiple organ failure (MOF) revealed endothelial inflammation in all affected organs (lung, kidneys, intestinal mucosa and heart) and in altered ECs suggesting a direct involvement of the virus in the disease onset of endothelial dysfunction [141]. This endothelial dysfunction could generate a systemic procoagulant state in addition to specific organ damage.

ECs likewise contributed to regulate blood flow due to their ability to inhibit thrombogenicity; therefore, blood components pass easily through the vascular system [142]. In pathophysiological situation such as an induced hyper-inflammation with SARS-CoV-2 infection, ECs switch to generate an anti-fibrinolytic and prothrombotic microenvironment and mainly participate in thromboembolism [142]. These events are assimilated to those observed in the current pandemic where the renin angiotensin aldosterone system (RAAS) is intrinsically associated with the coagulation pathways and may drive microthrombi development in COVID-19 positive individuals by enhancing of the immuno-thrombosis process [143].

Different mechanistic explanations in relation to EC can be put forward regarding the relationship between hypercoagulability and the immuno-pathogenesis of COVID-19 (Fig. 4):

- Ang II induces the release of TF and plasminogen activator-1 inhibitor (PAI-1) by ECs via the AT-1R receptor (angiotensin-type -1 receptor), this contributes to an imbalance the PAI-1/tPA ratio marked by a high coagulability and deposits of unresolved thrombus in alveoli of patients suffering from ARDS and pulmonary thromboembolism in COVID-19 individuals [145].

- The up regulation of released TF from ECs leads to the formation of TF-FVIIa complex and activation of the extravascular blood clotting pathway. This activation generates a direct release of thrombin from FII and leads to thrombus deposits in numerous tissues particularly the lungs [146].
- The elevated amounts of both factors vWF and FVIII linked to a significant endothelial inflammation [147].
- Various pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) are activated due to the injury of ECs [148]. These pro-inflammatory mediators contribute to microvasculature plugging and thromboembolism in lungs.
- ACE metabolizes bradykinin which stimulates vasodilatation and release of tPA from ECs as do BBPs from snake venoms [78, 133, 143].

Several other studies reported the involvement of elevated Ang II as a major mediator in coagulopathy associated with COVID-19. According to Stoll and collaborators [149], Ang II stimulated the increase in aldosterone which further improved the activity of ACE and attenuated the increase in tPA mediated by bradykinin. Hyper-aldosterone appears to correlate with the levels of PAI-1 and directly increases the expression of PAI-1 [150]. Although bradykinin may be elevated, the increase in ACE, Ang II and aldosterone will likely be more marked, with reduction in the tPA to PAI-1 ratio leading to fibrinolysis prevention [151]. Besides the generation of microthrombi as a general feature of COVID-19 patients, the imbalanced ratio of tPA versus. PAI-1 may be correlated to significant pulmonary thrombosis [145].

5 Cytokine Storm and Complement System: Interaction Between Inflammation and Coagulopathy in COVID-19

Several studies revealed the close relationship between thrombosis disorders and inflammatory response in COVID-19, which called thrombo-inflammatory response. There is a direct link between the innate immune system and hemostasis related to a hyperinflammatory profile that promotes endothelial dysfunction and induces a prothrombotic state. During disease, clots are formed through a thrombo-inflammation process involving thrombocytes, factors of coagulation and some effectors of innate immune system (macrophages, polynuclear neutrophils and the complement), [152, 153].

Many associated patholological events occurred simultaneously when ACE2 is inhibited due to SARS-CoV2/ACE-2 receptor attachment leading to an uncontrolled and widespread immunothrombosis and microangiopathy. These events contribute to progression to COVID-19-induced ARDS [153]. In infected patients with SARS-CoV2, many events such as vasoconstriction [154], proinflammatory cytokine profile and C-reactive protein [155] [156], pulmonary fibrosis [145] and DIC [139] participated together to induce ARDS evolution [157].

Both IL-6 and TNFα are involved in DIC that causes coagulopathy in sepsis due to inappropriate mechanisms of anticoagulation (antithrombin, tissue factor pathway inhibitor (TFPI) and the protein C system) and inactivated fibrinolysis with the high levels of PAI-1 [158]. In COVID-19, a cytokine storm characterized by deadly hyper-cytokinemia leads, in most cases, to multi-organ dysfunctional syndrome [159].

With regards to vascular complication associated with COVID-19, coagulopathy seems to be driven by pro-inflammatory cytokines [160] known as cytokine storm that is characterized by deadly hyper-cytokinemia and leads, in most cases, to multi-organ dysfunctional syndrome [143]. Pro-inflammatory cytokines may also induce the release of vWF, production of TF and FVII/FVIIa leading to increased thrombin generation, and decreased levels of endogenous anticoagulants [160]. Otherwise, the increased procoagulants combined to decreased anticoagulants, preventing resulted thrombolysis in the broad interchange between ECs, platelets, complement system, macrophages, polynuclear neutrophils and hemostasis process. The initiation of extravascular blood clotting pathway by TF released by ECs results from inflammation [153]. Intravascular blood clotting pathway initiated by FXII, and KKS is also triggered. All these events evidenced that thromboembolic disorders and particularly pulmonary embolism are driven by hyperinflammation through cytokine storm.

The IL-6 is associated with severity in COVID-19 pathogenesis; it appears to be involved in the high expression of the serum ferritin which is also a biomarker of the severity of COVID-19 [43]. In addition to IL-6, various increased inflammatory mediators of Th-1 pathway such as IL-1β, IL-12, IL-18, IL-33, CCL2, CXCL10 and TNF-α are found in severely infected individuals [43].

Two signalling pathways may explain the role of IL-6 during cytokine storm in COVID-19:

- Cis signaling in which the attachment of IL-6 to its receptor and gp130 downstreams the Janus kinases' signal transducer [161].
- Trans signaling, the binding of IL-6/soluble IL-6 leads to the release of IL-8 and vascular endothelial growth factor (VEGF) whereas it downregulates the expression of E-cadherin ECs [161].

Several studies reported the pivotal role of the complement system as potentiating event of thrombo-inflammation associated with SARS-CoV-2 infection [162, 163]. In the innate immune system, components from the system of

complement circulate in inactive form until they are needed. In COVID-19 pathogenesis, the complement system is responsible for triggering inflammo-thrombosis due to its role of opsonising pathogens. The crosstalk between the complement and coagulation systems was reported in many studies which revealed that the thrombotic complications in COVID-19 are related, in part, to complement activation [163]. The complement system can be activated at least by one of three pathways (classical, alternative and lectin pathways). The complement system induces a cascade of events generating some components (C3a, C5a and, MA; membrane attack complex) [164].

Once activated during thrombo-inflammation associated with COVID-19, the components of complement system such as C3a, C5a MASP-1 and MASP-2 contribute to the:

- Dysregulation of neutrophilia, endothelial dysfunction, and hypercoagulability.
- Degranulation and recruitment of macrophages and mast cells [164].
- Platelets activation and ECs, increasing TF and vWF expression [164].
- Generation of thrombin and fibrin from prothrombin to and fibrinogen respectively [165].

On the other hand, the close relationship between coagulation and complement pathways might be additionally upgraded by some activated factors of coagulation which can directly interact with components of complement (C3 and C5) [165].

6 Role of Platelets in Cytokine Storm and Mechanisms of Thrombosis in Severe COVID- 19

Thrombocytopenia appears to be a determinant predictive element for the COVID-19 severity while lymphopenia is believed to be a result of a failing immune response to SARS-CoV-2 [166]. At the same time, thrombocytes, well-known cells in hemostasis also significantly evolved pro-inflammatory role which enhances the resulting thrombo-inflammation in COVID-19 illness through direct or indirect hyperactivation of platelets following viral infection [167]. Both ventilation and SARS-CoV-2 infection disrupt lung-endothelium resulting in platelet hyperactivation since about the half of total platelets is produced in lungs, this makes pulmonary parenchyma vulnerable to directly high infectivity and inflammation. Ultimately, due to this hyperinflammation, a thickness in alveolar walls contributes to severe hypoxia [168].

Furthermore, during hemostasis process, the thrombocytes initiated the coagulation cascade that can be also stimulated by thrombin through PAR-1 and PAR-4 receptors. A surface of phospholipids (PLs) from thrombocytes once stimulated is required for the activation of several factors of coagulation at many stages of coagulation pathways [169].

Direct binding of coronavirus on platelets was previously reported with HCoV-229E antigens [170]. Based on the high similarity (~ 82%) between these both β-coronaviruses, Bhotla and collaborators proposed mechanisms of binding of SARS-CoV-2 on platelets that may elucidate the pulmonary embolism [171]. HCoV-229E interacts with the epithelial cells of lungs through the aminopeptidase N (CD13) as over-expressed receptors during viral infection [170]. Platelets also express CD13 of HCoV-229E as well as bone marrow cells; therefore, the virus entry is mediated through CD13 receptors. Once infected, bone marrow cells are dysregulated and lead to defective hematopoiesis resulting in thrombocytopenia [170].

Four mechanisms for thrombocytopenia associated with pulmonary embolism can be proposed [171], and outlined in Fig. 3B:

I. SARS-CoV-2/ACE-2R interaction induces the increase in Ang II which in turn interacts with TLR4 and degranulates thrombocytes.
II. SARS-CoV-2 may directly bind to FcγRIIA receptor.
III. The virus binds to CD13 of thrombocytes leading to the secretion of their granulations.
IV. Thrombocyte could serve as a virus production compartment; they make endocytosis of viral genomes and use their stored mRNAs for translation.

Through analogy, hypothetical mechanisms of thrombocytopenia associated with COVID-19 pathogenesis were reported [166]:

- Inhibition of platelet synthesis due to a direct infection of bone marrow cells.
- Destruction of platelet by the immune system.
- Aggregation of platelets in the lungs leading to increase of their consumption.

Among the various Toll-like receptors (TLR) expressed by platelets, the TLR-4 was reported to be the target receptor for Ang II and contributed to the pro-inflammation, functional impairment of pulmonary platelets and triggering their degranulation [172]. Other reported mechanisms relative to thrombocytopenia focused on the antiplatelet auto-antibodies that might be stimulated following inflectional process and can trigger destruction of platelets. Xu and collaborators put the hypothesis that the platelets predisposed to easy destruction by the reticulo-endothelial system due to deposition of immune complexes on platelet surfaces [166].

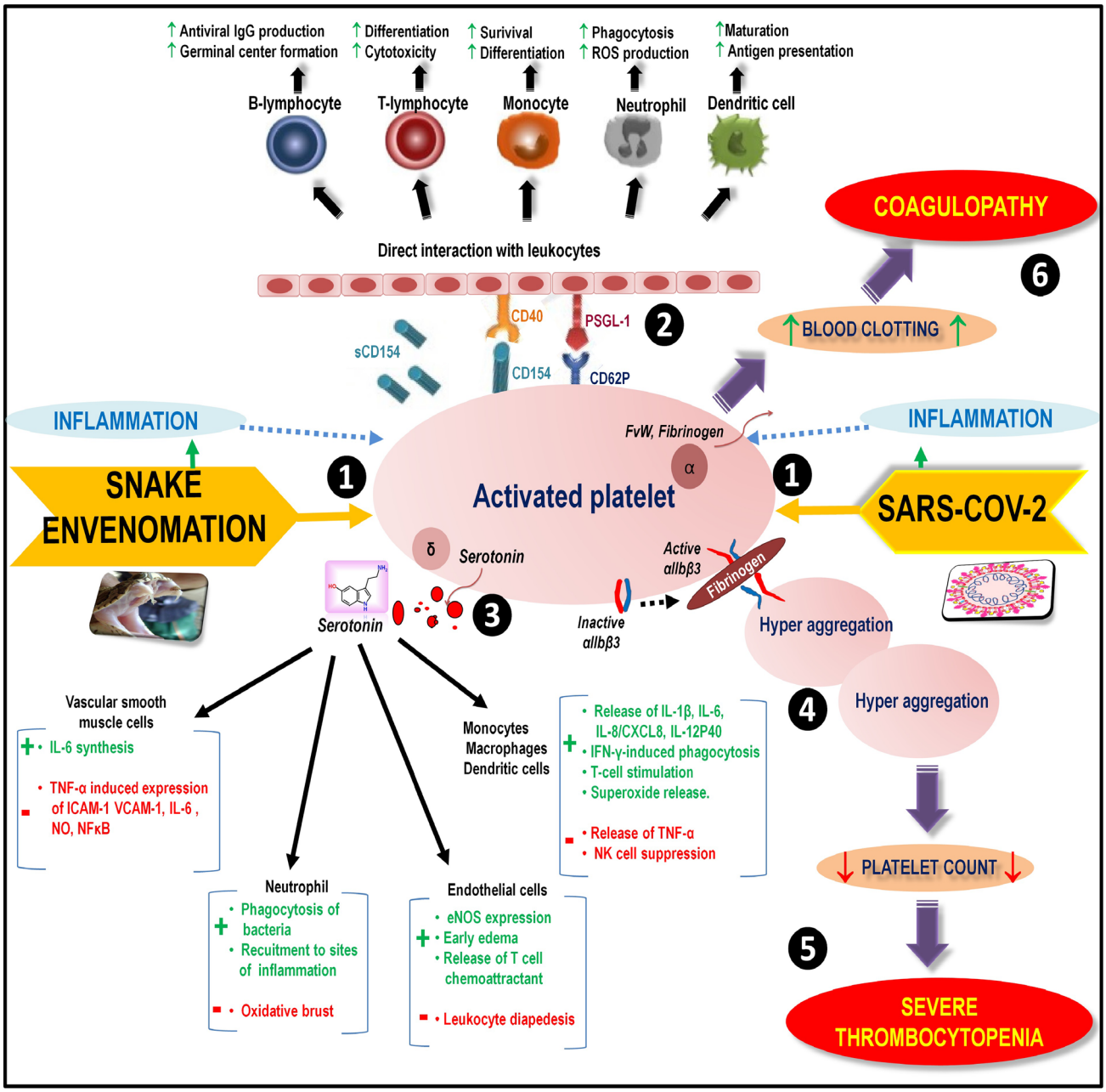


Fig. 5 Potential involvement of snake venoms and SARS-CoV-2 in hyperactivation of platelets and resulting thrombo-inflammatory complications. ❶ Direct action of targeted platelets by snake venom and SARS-CoV-2 inducing change in shape of circulating platelets, their spread and secretion of dense and α granulations. ❷ Direct interaction of activated platelets with leukocytes through expressed CD62P (P-selectin receptor) that binds to PSGL-1 and various leukocyte receptors, TLR4 promoted platelet and neutrophil interactions leading to neutrophil extracellular traps ❸ Platelet degranulation and release of serotonin that exhibits diverse proinflammatory effects. ❹ and ❺Hyperactivation of platelets and thrombocytopenia induced by snake envenomation and COVID-19.❻ Degranulation of α-granules of hyperactiveted platelets associated with snake envenomation and COVID-19 resulting in FvW and Fibrinogen release and coagulopathy [172, 173]

When activated, the platelet changes it shape and releases the stored components in its granules such as P-selectin, serotonin, cytokines and chemokines (Fig. 5). Because of their potential to release high amounts of pro-inflammatory IL-1β, the platelets are considered as a good source of this cytokine underling their role in the immune thrombotic process. Furthermore, α-granules contain a variety of immunostimulatory components that are activate and recruit macrophages and PMNs such as proplatelet basic protein, platelet factor 4 (CXCL4) and neutrophil-activating peptide-2 (CXCL7).

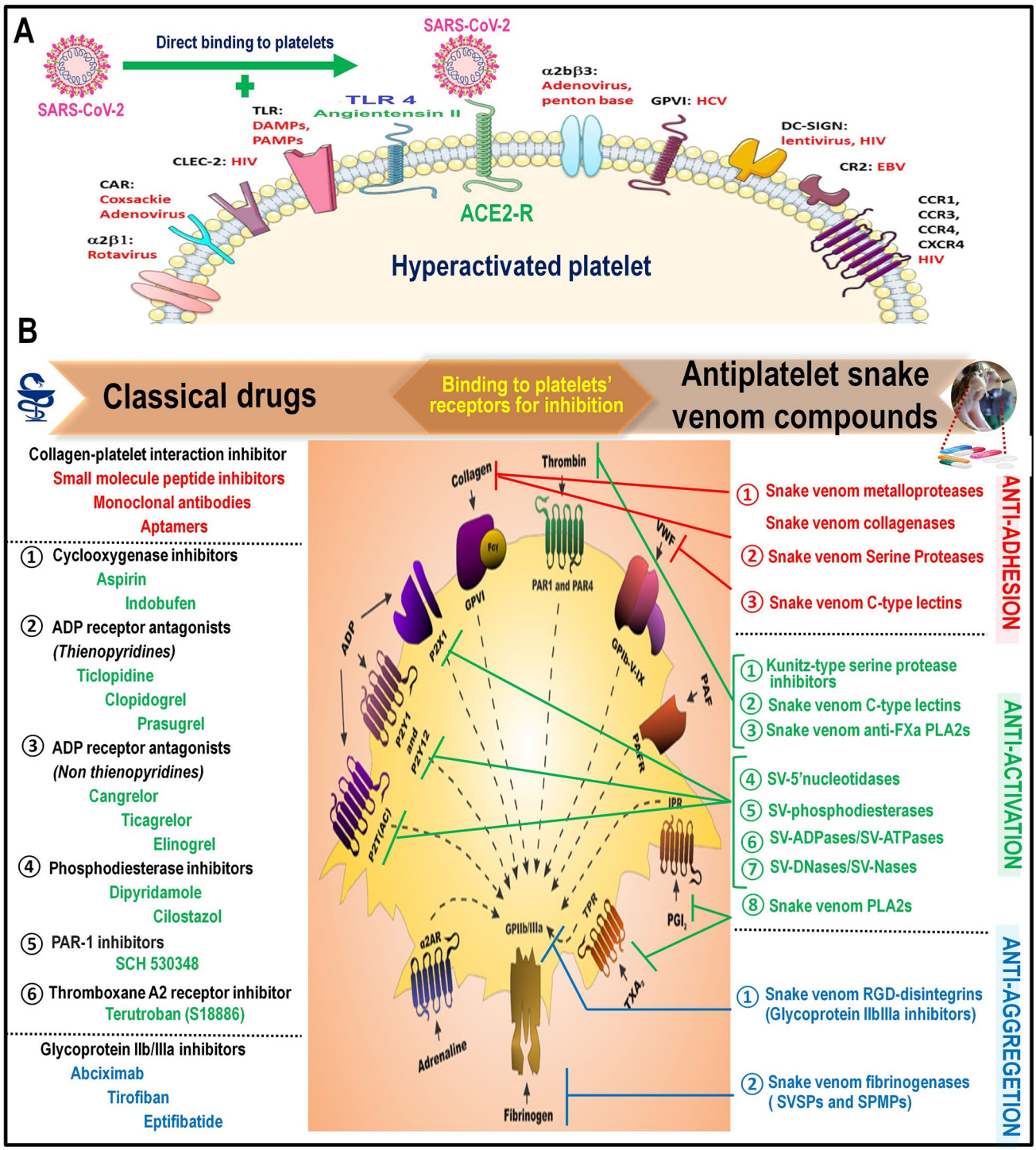


Fig. 6 Different platelet receptors and therapy. (A) Platelet receptors for several viruses including SARS-CoV-2 and ACE2. (B) Antiplatelet therapy, the receptors of platelets are the targets of venom proteins that inhibit platelet aggregation as well as conventional antiplatelet drugs [23, 177–179]

The recruited PMNs can undergo NETosis when stimulated by P-selectin that facilitates platelet-neutrophil complexes' formation [173].

It was reported that platelets expressed ACE2 and TMPRSS2 (Fig. 6A) [174]. Spike protein of SARS-CoV-2 is responsible for enhancing platelet activation at different stages (CD62P expression, α- and dense granules' release

and secretion and spreading of platelets), and thereby Spike protein enhanced thrombosis formation by facilitating the release of coagulation factors**.** These data may explain further the crucial involvement of hyperactivation of platelets in cytokine storm leading to thrombocytopenia and lung thromboembolism associated with COVID-19 pathogenesis.

COVID-19 is associated with coagulative disorders as patients have increased platelet activation and aggregation, and platelet-monocyte aggregation [175]. These coagulation disorders highlight the critical role of platelets in SARS-CoV-2 infection and immunopathology. Both platelets and megakaryocytes directly interact with SARS-CoV-2, raising the concern whether ACE2 receptor plays a role in this interaction. Abundance of ACE2 receptor and alternative receptors or co-factors for SARS-CoV-2 entry was characterized in platelets from COVID-19 patients and healthy persons as well as human megakaryocytes based on laboratory tests or previously reported RNA-sequence data. The results suggest that SARS-CoV-2 interacts with platelets and megakaryocytes via ACE2-independent mechanism and may regulate alternative receptor expression associated with COVID-19 coagulation dysfunction [176].

7 Therapeutics and Diagnostics Derived from Snake Venom Against a Wide Range of Diseases

Snake venoms are a mixture of bioactive compounds that were previously studied for their involved role in pathophysiological envenomation, while in recent years; they are explored for their potential use as new drugs as biotherapeutics for many public health concerns [9, 180]. Snake venom components are attracting the attention of pharmaceutical industry for their potential therapeutic values. Several snake venoms derived-drugs are either in clinical trials or in use (Table 2). Cobra venom was used already to treat inflammation, arthritis, joint pain, opium addiction or combined with opium to treat pain.

Snake venoms are a valuable bank of novel generation of principle components in drug discovery, nevertheless, only a limited number of components has been identified, from which some FDA-approved drugs are now used as medicine [28]. Some proteins and peptides derived from snake venoms are in preclinical phase or clinical trials to be used for some pathologies (Table 2).

7.1 Approved Drugs Derived from Snake Venom Peptides and Proteins as Possible Potential Anti-SARS-COV-2 Drugs

Snake venoms become a novel natural pharmacopeia to develop new drugs, since the approval of Captopril, the first antihypertensive snake venom-derived drug:

- Captopril® (FDA approval in 1981): The drug is a biomimetic of BBPs isolated from *Bothrops jararaca* venom (Brazil). It is used to treat high blood pressure with regard to its inhibitory potential on ACE [181]. Many derivatives of Captopril® have been successfully produced by Squibb and other companies and are being introduced into the market [182–184] (Table 2A). Snake venom BBPs could be effective drugs by decreasing the over expression of ACE-2. Captopril as an ACE inhibitor blocks the production of Ang II (a potent vasoconstrictor), and therefore leads to a decrease in arterial resistance. ACE (a zinc metalloprotease) releases Ang II from Ang I (inactive peptide) after peptide bond hydrolysis. The zinc atom of the active site plays a catalytic role by activating the water molecule. Captopril works by blocking the vacant coordination of zinc with its thiol function. Many BBPs such as BBP-10c have been isolated from snake venom [185]. BPP-10c strongly reduced Ang II by inhibiting ACE and increasing bradykinin-related effects on the bradykinin 2-receptor [185] (Table 2A).
- Aggrastat® (Tirofiban, FDA approval in 1998): Aggrastat® is extracted from Echis carinatus venom and belongs to disintegrins, it is an antiplatelet drug containing the RGD sequence (Arg-Gly-Asp) motif [186, 187]. Disintegrins are group of small peptides cysteine-rich and originally purified from the venoms of *Viperidae* snakes [188]. Tirofiban was originally developed by Merck but now it is marketed by Medicure Pharma in the US and Correvio International outside of the US (Table 2A).
- Integrilin® (Eptifibatide, FDA approval in 1998): Integrilin® (Eptifibatide, FDA approval in 1998): It isolated from the venom of Southeastern rattlesnake by Millennium Pharmaceuticals [186], this KGD (Lys-Gly-Asp)-disintegrin mediated platelet aggregation and, therefore, it treated individuals suffering from cardiovascular complications (unstable angina and myocardial infarctions and acute coronay syndrome) and prevented deadly heart attack in vulnerable patients [17, 189]. Eptifibatide is a GPII/bIIIa inhibitor obtained from *Sistrurus barbouri* venom, designed as peptide mimicking a small portion of barbourin, [190] (Table 2A). Several snake venom containing RGD-disintegrins are isolated and well characterized as effectively anticoagulant therapeutics and platelet inhibitors by targeting selectively GPIIb/IIIa

Table 2 Therapeutic and diagnostic compounds derived from snake venom and their possible therapeutic or diagnostic mechanism anti-COVID-19

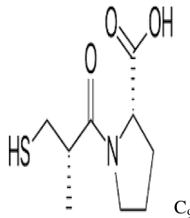
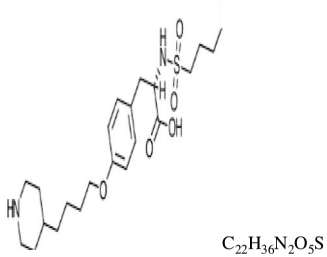
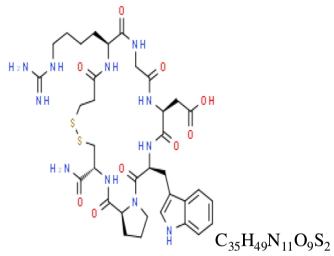
Drug name and references	Snake venom species	Molecular formula and structure	Diseases to treat	Possible use in COVID-19 therapy	
				Proposed mechanism as therapeutics	Proposed mechanism as diagnostics
A/Approved drugs derived from snake venoms as therapeutics					
Captopril® [181–184]	*Bothrops jararaca*	 $C_9H_{15}NO_3S$	Treatment of high blood pressure, renal disease in diabetics and heart failure after myocardial infarction	-Strongly decreases Ang II by inhibiting ACE - Increases bradykinin-related effects on the bradykinin 2-receptor -Increasing nitric oxide-mediated effects	
Aggrastat® (Tirofiban) [186–188]	*Echis carinatus*	 $C_{22}H_{36}N_2O_5S$	Reduce the rate of thrombotic cardiovascular events such as a heart attack	Inhibits with high affinity platelet integrin (GP) IIb/IIIa Prevents hyperactivation of platelets and thrombocytopenia Anti-pulmonary embolism	
Integrilin® (Eptifibatide) [186, 190, 191]	*Sistrurus miliarus barbouri*	 $C_{35}H_{49}N_{11}O_9S_2$	Treatment of patients with acute coronay syndrome to decrease the chance of a new heart attack or death, including patients undergoing percutaneous coronary intervention	-Mimicking a small portion of barbourin, a GPIIbIIIa inhibitor - Prevents hyperactivation of platelets and thrombocytopenia - Anti-pulmonary embolism	
Defibrase®/ Reptilase® (Batroxobin) [19, 184, 192]	*Bothrops atrox* and *Bothrops moojeni*		- Treatment of ischemic stroke, angina, myocardial and cerebral infraction and wound management after surgical interventions -Treatment of acute cerebral infarction, unspecific angina pectoris, and sudden deafness - Used to prepare autologous platelet-gel, an emerging biotechnology in current tissue engineering and cellular therapy	- An anticoagulant drug of relevance for treating thrombotic disorders, as the degradation of fibrinogen leads to defibrination - Induces the release of t-PA, converts plasminogen into plasmin and promotes the degradation of clots	
Viprinex® (Arvin/Ancrod)	*Calloselasma rhodostoma*		-As anticoagulant and indicated for the treatment of ischaemic stroke, myocardial infarction and deep-vein thrombosis - Potential benefit to patients suffering from heparin-associated thrombocytopenia and thrombosis syndrome	- Prevention of thrombocytopenia associated with severe COVID-19 - Potential antithrombotic and anti-myocardial infarction for patients vulnerable to side-effects of chloroquine	

Table 2 (continued)

B/Approved drugs derived from snake venoms as diagnostics			
Textilinin-1 [193]	*Pseudonaja textilis*	Anti-fibrinolytic drug Use for reducing blood loss associated with complex surgeries	Could be useful to control bleeding following anticoagulation therapy
Hempatch [184, 193]	*Pseudonaja textilis*	It was translated into novel therapeutics to control bleeding To control bleeding at sites of trauma or surgery, whereas the Factor Va-like protein, CoVase, is being assessed for its utility for combating non-compressible hemorrhage	Could be useful to control bleeding following anticoagulation therapy
Reptilase® (Batroxobin) [194, 195]	*Bothrops atrox* and *Bothrops moojeni*	-To measure fibrinogen levels and blood coagulation capability through the in vitro clotting time - Used also to detect antithrombin activity	Fibrinogen level testing for adequate and early management of individual with COVID-19
Pefakit® (RVV-V) [195–197]	*Daboia russelii*	Used to identify factor V levels in plasma Used in assays for the diagnosis of resistance to activated protein C, which does not cleaves factors Va and VIIIa Used to the diagnosis of lupus anticoagulant	These approved diagnostics derived from snake venoms could be used for testing hemostasis disorders associated with COVID-19 in order to early diagnose SARS-CoV-2 infection
Stypven® (RVV-X) [82, 195, 198]	*Daboia russelii*		
Ecarin [195, 199]	*Echis carinatus*		
Botrocetin® (Venom coagglutinin) [195, 200]	*Bothrops jararaca*	Platelet aggregation by increasing the affinity between the receptor GPIbα and von Willebrand factor	Identification of von Willebrand factor deficiency or activation during coagulopathy linked to COVID-19
Protac® [200]	*Agkistrodon contortrix contortrix*	Used to quantify protein S and C levels by prolongation of the activated partial thromboplastin time (aPTT) Investigation of the cause of a blood clot (thromboembolism), linked to deep vein thrombosis or pulmonary embolism	Direct testing of thromboembolism), linked to deep vein thrombosis or pulmonary embolism associated with COVID-19
MTα and KT-6.93 [201]	Mamba snake venoms	Studies of novel treatments for blood pressure disorders (MTα) blood coagulation disorders (KT-6.93)	Diagnosis of both COVID-19 complication; blood pressure disorders (MTα) blood coagulation disorders before and after treatment

integrin [202]. Antiplatelet therapy is needed to combat thrombocytopenia and severely complicated thromboembolic disturbances associated with COVID-19 pandemic. Disintegrins derived from snake venoms are potential candidates as antithrombotic therapeutics [202].

– Defibrase®/Reptilase® (Batroxobin, approved clinically in the US, but approved for use in other countries): Defibrase® also referred as to Reptilase® (Batroxobin, approved clinically in some countries including USA): This drug is a SVSP derived from two bothroptic venoms (*Bothrops atrox* and *Bothrops moojeni*) [192]. Batroxobin, as several SVTLEs is α fibrinogenase releasing only fibrinopeptide A upon cleavage of the α -chain of fibrinogen whereas its β -chain remains uncleaved [184]. Such SVTLEs are not sensitive to physiological serine protease inhibitors [19, 184]. Cerebral and myocardial infarction, ischemic stroke and angina are the main diseases that are currently treated by Defibrase® [78]. Batroxobin drug is now commercialized with different names:
– Batroxobin and Reptilase (Tobishi Pharmaceutical, China) [203].
– Defibrase (DSM Nutritional Products Ltd Branch Pentapharm, Switzerland) and Botropase (Hanlim, South Korea)[203].
– Botroclot (Juggat Pharma, India) [203].
– Plateltex-Act® (Czech Republic) [204] and Vivostat System (Denmark)[205]. Both of them are valuable biotherapeutics and currently served as tools as autologous platelet-gels in cellular therapy [206, 207].

Batroxobin, is widely utilized for perioperative bleeding and as effective and safe bio-drug for array illnesses including pulmonary embolism and deep vein thrombosis [28]. This opens prospect to introduce Batroxobin in therapeutic strategy anti- COVID-19 aiming to prevent the fatal pulmonary embolism often associated with severe individual infected by SARS-CoV-2.

– Viprinex® (Arvin/DrugBank Accession Number DB05099): a SVSP commonly known as Ancrod that previously identified in *Calloselasma rhodostoma* venom. Pharmacologically, Viprinex® displays defibrinating effect resulting from the proteolysis of fibrinogen. Thusly, the therapeutic indications of this anticoagulant drug include ischemia, deep-vein thrombosis, myocardial infarction and individuals present with thrombocytopenia [208, 209]. The anticoagulant effects of Ancrod are due to the rapid removal of fibrinogen from the blood within hours following drug administration. Ancrod specifically cleaves only the α-chain of fibrinogen, producing only the fibrinopeptides A. The resulting fibrin polymers are imperfectly formed and much smaller in size (1 to 2 μm) than that produced by thrombin. These ancrod-induced microthrombi do not cross-link to form thrombi as they are friable, unstable, urea-soluble and significantly degraded α-chains. These microthrombi are markedly hydrolyzed by plasmin and are rapidly removed from circulation by either reticulo-endothelial phagocytosis or normal fibrinolysis, or both. Blood viscosity is reduced by 30–40%.

Furthermore, Ancrod does not activate Factor XIII and plasminogen; it does not degrade the preformed and fully cross-linked fibrin as thrombin. Consequently, unlike fibrinolytic agents, Ancrod can be used post-operatively. This venom-derived drug induces platelet aggregation, the release of ADP, ATP, potassium and serotonin from platelets [209].

7.2 Diagnostic Tool Derived from Snake Venom Peptides and Proteins for Testing Coagulopathy Associated with COVID-19

Snake venom peptides and proteins are not only used therapeutics but a number of them are valued as successful biodiagnostics for three decades (Table 2B).

- Textilinin-1 (commercialized under the moniker Q8008): derived from *Pseudonaja textilis* venom, is a specific inhibitor peptide of plasmin. It presents properties as an anti-thrombolytic potential. This peptide is applied to reduce blood loss resulting in complex surgeries [193] (Table 2B).
- Hempatch: identified in the venom of *Pseudonaja textilis,* it combines both FXa- and FVa-like factors with its dual potentials, it is a used in translational medicine (Table 2B). Hempatch (control bleeding tool) and CoVase (anti-hemorrhagic agent) are given names to FXa-like and FVa-like proteins respectively [184, 193].
- Reptilase®: the unique approved drug from snake venoms used as dual agents (therapeutics and diagnostics). Reptilase® is applied as a laboratory reagent instead of thrombin to quantify fibrinogenemia and to diagnose coagulation disorders (Reptilase® time), [194]. Reptilase® test presents an interest as it does not require cofactors (phospholipids and Calcium), leading to prohibit platelet aggregation and inactivate platelet dependent-coagulation factors [195].
- Pefakit®: this reagent is also referred to as RVV-V. The venom of *Daboia russelii* is a rich source of SVSPs from which Pefakit® has been characterized as a FVa-like protease (27 kDa) [196]. To date, laboratories perform Pefakit® test to diagnose patients present with resistance

to activated protein C and lupus anticoagulant characterized by the presence of antiphospholipid antibodies [195–197] (Table 2B).

- Stypven®: RVV-X is a macromolecule with 120 kDa isolated from *Daboia russelii* venom and capable for inducing a direct FX activation [82, 198]. This protein requires cofactors (Ca2 + , FV, phospholipids and FII) to be activate [195]. Stypven® is also used as Pefakit®, to diagnose patients suffering from the manifestations of antiphospholipid syndrome [195].
- Ecarin: A metalloprotease prothrombin activator purified from the venom of Echis carinatus. Ecarin is a very useful reagent since it acts without any cofactors for thrombin clotting assay [195]. Ecarin test is used to detect different abnormal types of FII [199]. Ecarin, such as Stypve^{n}® and Pefaki^{t}®, is the third snake venom derived-diagnostics drug that is used for lupus anticoagulant diagnosis (Table 2B).
- Botrocetin®: Also termed ''Venom coagglutinin'', is a C- type lectin-like protein (22 kDa) purified from the venom Bothrops jararaca. Botrocetin® mediates the platelet aggregation by binding to GPIbα and enhancing the affinity to its ligand vWF [200].
- ACC-C (Protac®): obtained from Agkistrodon contortrix venom [210]. It is an activator of protein C. which interact with protein S and C to quantify their plasma levels. Protac®. Protac® assay presents a significance since AAC-C activity is not affected by protein C plasma inhibitors [195]. Protac® depends on the prolongation of aPTT to investigate the cause of thromboembolism associated with deep vein thrombosis [210]
- MTα and KT-6.93 are small peptides members of Three-Finger Toxins' family. Both compounds have been utilized in biodiagnostics of blood pressure and disorders associated with blood coagulopathy [201] (Table 2B).

8 Anti-SARS-CoV-2 Therapeutic Possibilities from Snake Venom Compounds

There are various on-going active clinical trials to potentially treat SARS-CoV-2 under investigations across the world. No clinical trials have confirmed significant efficacy against SARS-CoV-2 including anti-malarial and anti-retroviral agents [163].

Further, clinical trials on the plasma of patients and the antibodies anti-SARS-CoV-2 were not effective. These failed trails of treatments against COVID-19 gave rise to the need to investigate for natural compounds. Snake venoms could present a potentially valuable resource of pharmacological agents in the management of this pandemic disease.

8.1 Defibrinating, Anticoagulant and Thrombolytic Snake Venom Compounds

8.1.1 Defibrinating and Thrombolytic Thrombin-Like Enzymes

SVTLEs are assimilated to thrombin due to their ability to clot plasma by cleaving fibrinogen [8]. Whereas, unlike thrombin, these serine proteases are not able to activate FXIII required for stabilizing formed thrombus. In this case, the produced clots by SVTLEs are unstable and easily cleared [127, 211]. These characteristics make SVTLEs good candidates as lead bio-compound therapeutics or diagnostics to dissolve undesirable embolus resulting in platelet hyperactivation and coagulation associated with COVID-19 pathogenesis.

Our group has previously reported a variety of SVTLEs identified and purified from snake venoms, their interesting pharmacological potentials were also characterized (Table 3). SVTLEs are classified into three families, according to the released fibrinopeptide (FP), (i) α- fibrinogenases releasing the FPA of the Aα chain of fibrinogen, (ii) β-fibrinogenases releasing the FPB of the Bβ chain of fibrinogen and (iii) α,β-fibrinogenases cleaving both fibrinogen chains. However, they usually release either FPA or FPB similar to thrombin [30, 128]. They inhibit and/or activate platelet aggregation and/or blood coagulation and exhibit a potential pharmacological antithrombotic effect.

Moreover, pro-platelet SVSPs act directly on platelet receptors promoting the formation of bridge between platelets which is the result of fibrinogen binding to GPIIb/IIIa integrin [127]. These anticoagulant SVTLEs may activate also Protein C, which in turn prevents the activation of FVa and FVIIIa [128]. Thrombolytic SVTLEs are also able to activate the plasminogen activators (t-PA) to eliminate the produced thrombus, this leads to attenuate coagulopathy [30, 129].

Despite their fibrinogenase activity, SVTLEs are anticoagulant agents that can be used as therapeutic agents to treat thrombosis associated with COVID-19 pandemic. The cleavage of fibrinogen by SVTLEs leads to defibrination which can be enhanced as they exhibit plasmin-like activity [184].

Several studies on SVTLEs have reported their thrombolytic role suggesting a direct action on vascular endothelial cells promoting the release. This effect may potentially be interesting in their possible use as anticoagulants for COVID-19 pandemic (Fig. 7, Table 3).

8.1.2 Snake Venom Kunitz-type inhibitors as potential blockers of SARS-CoV-2 Entry

Kunitz-type peptides are the smallest components found in the snake venoms, their length comprise of about 50 to

60 amino acid residues. Kunitz-type peptides can interact with an array of serine proteases and inhibit their catalytic site, they are also called bovine pancreatic trypsin inhibitors (BPTIs) [212]. These characteristics make snake venom BPTIs as potential antiviral agents when target TMPRSS2 activity required for SARS-CoV-2 entry.

Treatment of patients with the snake venom BPTIs could block the entry of SARS-CoV-2 and prevent inflectional process. Several BPTIs have been found in snake venoms (Fig. 7, Table 3B). In envenomed victims, BPTIs impaired hemostatic system and block potassium channels [213], or both [214]. Thus, snake venom BPTIs may have dual interests as anti-SARS-CoV-2 as anticoagulant and inhibitors of TMPRSS2.

8.1.3 Anticoagulant PLA2s

Some snake venom PLA2 (SV-PLA2) inhibit blood coagulation [215, 216]. They are classified into coagulant (strong or weak) or anticoagulant. Many coagulation factors need phospholipids for their activation and interaction between each other. Thus, SV-PLA2 exhibit anticoagulant effects through an enzymatic mechanism by hydrolyzing phospholipid surfaces, subsequently, the prevent platelet activation and inactivation of coagulation cascade [128]. Additionally, strong anticoagulant PLA2 are able to inhibit coagulation through non-enzymatic mechanism since they are capable to selectively target and bind to FXa with high affinity, thereby, SV-PLA2 inhibit prothrombinase complex and prevent thrombin generation [217].

Another mechanism of anticoagulation underlined by almost all SV-PLA2 inhibit the extrinsic tenase complex (TF–FVIIa), [218]. Both enzymatic and non-enzymatic mechanisms that allow to inhibiting the tenase complex give a rise evidence on the strong role of SV-PLA2 as strong anticoagulant. This promising anticoagulant potential leads to an application of SV-PLA2 as anticoagulant agents in COVID-19 therapy (Fig. 7, Table 3A).

8.2 Antiplatelet Snake Venom Compounds

8.2.1 Disintegrins, C-Type Lectins and Three-Finger Toxins (FTX)

Snake venoms contain also non-enzymatic components represented by C-type lectin-related proteins that were the first peptides to be identified as potent anticoagulant and antiplatelet compounds [219, 220]. C-type lectin-related proteins interact directly with some factors of coagulations such as FIXa, FXa and thrombin or through binding on platelet receptors [221, 222]. Structural modeling and mechanism of action of C-type lectins have revealed their potential antiplatelet activity such as Cc-Lec [24] (Fig. 6B, Fig. 7, Table 3B). The formation of the platelet-platelet bridge is mediated by the binding of fibrinogen to its GPIIb/IIIa receptor also referred to as αIIbβ3 integrin [202]. It has been considered as a pharmacological target in the therapy of thrombosis diseases, due to the role of this receptor in the platelet aggregation.

Many GPIIb/IIIa inhibitors such as Tirofiban and Eptifibatide are developed from snake venoms and commercialized for patients with acute coronary syndrome or undergoing percutaneous coronary interventions [186]. Further, several $\alpha_{IIb}\beta_3$ integrin blockers from snake venoms were reported (Fig. 6B, Fig. 7, Table 3B).

The anticoagulant and antiplatelet effects of three-finger toxins were the first identified cardiotoxin isolated from *Naja nigricollis* venom [223, 224]. The mechanism of antiplatelet action of these cardiotoxins has been well elucidated [225]. Several 3-FTX anticoagulant and antiplatelet effects have been characterized (Table 3B).

8.2.2 Nucleotidases, Phosphodiesterases and Nucleases

Nucleotidases and phosphodiesterases of snake venoms are phosphate-releasing enzymes that exhibit dual anti-platelet and anti-thrombotic activity. However, they do not directly interact with platelets but rather cleave ADP to AMP and phosphate. The released phosphate, in turn, binds to A2 platelet receptor and inhibits aggregation. Several members of enzymes have been characterized from snake venom as antiplatelet agents [23, 228] (Table 3B).

Snake venom derived-compounds may be used for treatment of coagulopathy associated with COVID-19 as an alternative to the other conventional anticoagulant drugs. They are natural molecules with less side-effects which make them superior to synthetic drugs. As mentioned in Table 3A, 3B and 3C, the drug-induced immune thrombocytopenia and severe reactions are the most severe side effects of Tirofiban and Eptifibatide as αIIbβ3 antagonists [244]. The thrombocytopenia was restored by Tirofiban and Eptifibatide two weeks post-treatment. However, this thrombocytopenia persists when thienopyridines (Ticlopidine, Clopidogrel, Prasugrel), non-thienopyridines (Cangrelor, Ticagrelor, Elinogrel) and PDE inhibitors (Dipyridamole, Cilostazol) Abciximab (chimeric 7E3 Fab) are used. Therefore, the thrombocytopenia and gastrointestinal bleeding may not be restored by these drugs [230, 231]. Relative to heparin (Table 3C), some well-documented issues are related to its clinical application such as its inefficacy in anti-thrombin deficient patients, bleeding complications and heparin-induced thrombocytopenia as severe side effects [280].

Table 3 Summary of potential antiviral/anti-thrombotic therapeutic compounds derived from snake venoms on COVID-19 and their multiple molecular targets and receptors compared to conventional drugs

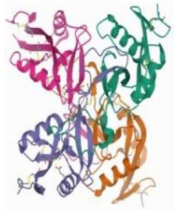
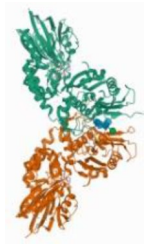
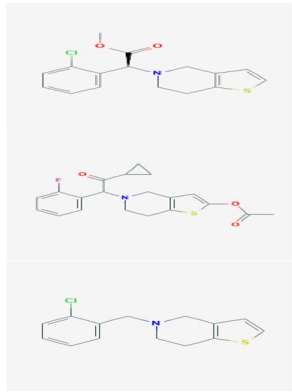
Virus and molecular targets	Mechanism of action of snake venom compounds				Conventional drugs		
	Families of snake venom compounds	Snake venom compound and references	Scaffold structure	Potential anti-COVID-19 mechanism	Drug name	Structure	Side effects and drug resistance
Platelet receptor activators	A/Indirect antiplatelet effects						
von Willebrand Factor (vWF)	C-type lectins	Botrocetin[177], bitisicetin [178]	 1FVU.pdb	Inhibition of the interaction between vWF and GPIb, leading to less platelet adhesion and less thrombus formation The absent procoagulant activity of platelets (which serve as surface for the assembly of coagulation complexes) reduces coagulation, resulting in less thrombin generation and consequently results in less fibrin(ogen) formation			
ADP	5'NTase	VL-5'-NT [229]; Cc-5'NTase [23]	5H7W.pdb 	Direct inhibition of both ADP- and arachidonic acid-induced platelet aggregation by converting ADP to adenosine, activating specific subtypes of P1 receptor and mediating inhibition of thrombosis associated with COVID-19 pathogensis	*Thienopyridines* Ticlopidine Clopidogrel Prasugrel		Thrombocytopenia and gastrointestinal bleeding [230, 231]

Table 3 (continued)

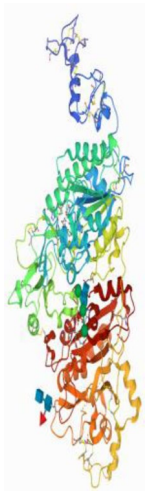
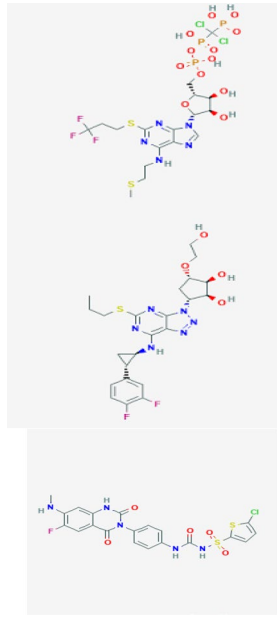
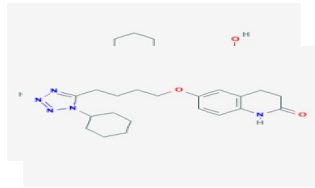
Virus and molecular targets	Mechanism of action of snake venom compounds				Conventional drugs		
	Families of snake venom compounds	Snake venom compound and references	Scaffold structure	Potential anti-COVID-19 mechanism	Drug name	Structure	Side effects and drug resistance
ADP	PDEs/ ADPase/ RNase	DR-PDEof Daboia russelli russelli[226], PDE-I of Agistrodon bilineatus[232], PDE of Crotalus ruber ruber [233], NPP-BJ of Bothrops jararaca[234]. VL-PDE of Vipera lebetina venom [227], Cc-PDE of Cerastes cerastes [228]	 5GZ4. pdb	Snake venom RNases disturb genomic RNA of SARS-CoV-2 exhibiting antiviral action by affecting viral RNA replication and translation The interaction of SV-PDEs with blood coagulation is related to ADP hydrolysis leading to the inhibition of its interaction with specific receptors including P2Y12	*Non thienopyridines* Cangrelor Ticagrelor Elinogrel		Thrombocytopenia and gastrointestinal bleeding [230, 231]
	Three-finger toxins	KT-6.9 Similar to UniProtKB number P60305, *Naja kaouthia* [179]	3HH7. 	Possibly binds to platelet P2Y12receptor Inhibit platelet activation mediated through P2Y12receptor	*PDE inhibitors* Dipyridamole Cilostazol		

Table 3 (continued)

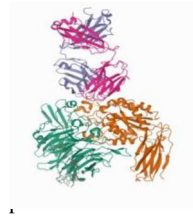
Platelet receptors	B/direct antiplatelet effects						
αIIb/β3 (ITGA2B/ITGB3)	Disintegrin and disintegrin domains of SVMPs	Applagin [235, 236], saxatilin [237, 238], elegantin [239], flavoridin and kistrin [240], CCSV-MPase[74], Disintegrin-Cc [241], Cerastategrin [202]	1J2L.pdb 	Prevention of fibrinogen binding to platelets and inhibiting platelet aggregation The antithrombotic strategy selectively inhibiting outside-in signaling without causing integrin activation nor affecting the processes of primary hemostasis, thus they do not increase bleeding risk and have greater safety profiles	Abciximab (chimeric 7E3 Fab)	6V4P. 	Thrombocytopenia and gastrointestinal bleeding [230, 231]
αIIb/β3 (ITGA2B/ITGB3)	Three-finger toxins	Dendroaspin, *Dendroaspis jamesoni kaimosae* (also named mambin; UniProt KBP28375) [242], S5C1 (UniProt KB number P01413) *Dendroaspis jamesoni kaimosae* [243], Thrombostatin, (UniProtKB P81946), *Dendroaspis angusticeps*	1DRS.pdb 	Binds to platelet integrin αIIbβ3 and inhibits platelet aggregation mediated through interactions between integrin αIIbβ3 and fibrinogen	Tirofiban Eptifibatide	(Illustrated in Table 2)	Drug-induced immune thrombocytopenia and severe reactions to re-administration are the most severe side effects of αIIbβ3 antagonists[244]. However, thrombocytopenia restored two weeks post-treatment
GPIb (GPb1)	C-type lectins	Echicetin [245], agkicetin [246], and flavocetin-A [247] Anfibatide (trade name of agkisacucetin [248]	1OZ7.pdb 	GPIb, receptor of vWF, an effective target for inhibition of platelet adhesion in antithrombotic therapy GPIbα blockade by anfibatide treatment could be useful in ischaemic stroke through inhibition of thrombosis	Monoclonal antibodies Aptamers		

Table 3 (continued)

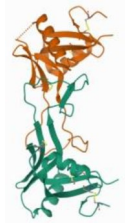
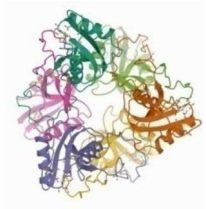
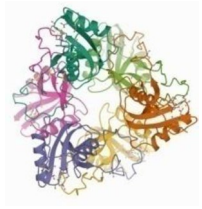
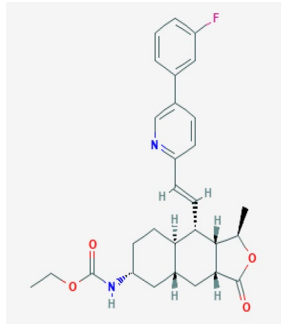
Platelet receptors	B/direct antiplatelet effects					
α2/β1 (ITGa2/ITGb1)	Disintegrin like-domain of SVMPs	Trigramin [249–251], bitistatin [252, 253]	2MOP.pdb 	Platelet inhibition via interactions with α2β1 integrins; resulting in the inhibition of collagen-stimulated platelet aggregation and prevention of thrombocytopenia associated with COVID-19		
	C-type lectins	Rhodocetin [254, 255] alboaggregin A [256], alboluxin [257, 258]; bilinexin [259]	1SB2.pdb 			
GPVI	SVMPs (Collagenases)	Alborhagin[260] Crotarhagin [260] Atroxlysin-III [261]	1WNI.pdb 	Cleavage of glycoprotein VI (GPVI) into a soluble ~ 55-kDa fragment (sGPVI). Thereby, inhibition of of platelet aggregation Targeting GPVI antagonistically contributes to the antithrombotic effect needed in COVID-19 therapy		
PAR-1/4	C-type lectins (Anti-FXa/FIXa)	Bothrojaracin[262], Cc-Lec [24]	1IXX.pdb 	Anticoagulant function of great therapeutic value, related to the their interaction with coagulation factors FXa and/or FIXa Prevention of thrombin generation and antiplatelet by PAR-1/4 blockade	*PAR-1 inhibitors* Vorapaxar (SCH 530,348)	

Table 3 (continued)

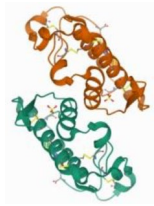
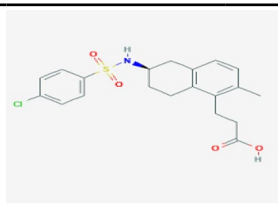
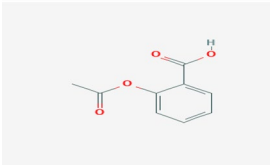
Platelet receptors	B/direct antiplatelet effects					
TPα	PLA2	Cc1-PLA2 [263]; Cc2-PLA2 [20]	3G8G.pdb 	Strongly anticoagulant tby inhibition of the tenase by both enzymatic and non-enzymatic mechanisms. This promising anticoagulant activity of SV-PLA2 leads to a possible application as anticoagulant agents in COVID-19 therapy	Thromboxane A2 receptor inhibitor Terutroban (S18886) Aspirin	 
Coagulation pathways	C/anticoagulant and thrombolytic effects					
Fibrinogen	SVTLEs (Fibrinogen-ases)	Cc_3-SPase[211, 264–266] flavoxobin [267]batroxobin[268], ancrod[269], proteinase RP34[8], cerastotin [270], BJ-48[271], leucurobin [272]	1OP0.pdb 	Consumption of clotting factors and hypofibrinogenemia leading to thrombus prevention		

Table 3 (continued)

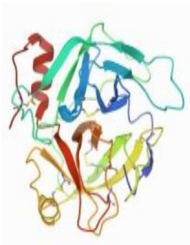
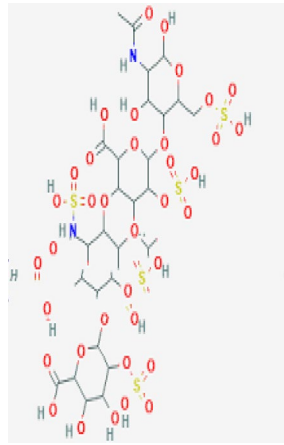
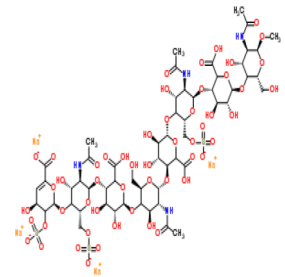
Coagulation pathways	C/anticoagulant and thrombolytic effects						
Thrombin and FXa Thrombin and FXa	SVTLEs (Fibrinases)	BjussuSP-I [273], agacutin [274], purpurase [275]and pictobin[276]. Crotalase[277], gabonase[277], cerastobin [278] Afaâcytin [8]Fibrolase [279]	4GSO.pdb 	No stimulatation of FXIII to cross-link fibrin polymers resulting in unstable clots readily dissolved by plasmin Ultimately, the continual generation and destruction of fibrin thrombi results in a consumptive coagulopathy that depletes fibrinogen physiologically and could be of great therapeutic way anti-COVID-19	Heparin		Some well-documented problems related to its clinical application such as its inefficacy in antithrombin deficient patients, bleeding complications and heparin-induced thrombocytopenia as severe side effects [280]
					Enoxaparin sodium		

Table 3 (continued)

Coagulation pathways	C/anticoagulant and thrombolytic effects				
Fibrin Fibrin	Three-finger toxins	Exactin (UniProtKB number P0DQH2, Hemachatus haemachatus) [281] Ringhalexin (UniProtKB number C0HJT, Hemachatus haemachatus) [282]Najalexin UniProtKB number Q9W717 Naja atra [283], Ophiolexin UniProtKB number V8N9N7 Ophiophagus hannah [283] Hemextin AB complex UniProtKB number P0DQH3, P0DQH4, *Hemachatus haemachatus* [284]	3VTS.pdb 	Binding toandinhibitionFVIIa-TFinteractionswithouttheneedforsubstrate(FX) Attenuation of the initiation ofcoagulation Blockade of extrinsic coagulation pathway Hyperactivated resulting in endothelial dysfunction associated with COVID-19, leading to thromboembolic disorders and lung embolism	
TARGETED VIRUS	D/Antiviral effect				E/Anti-SARS-CoV-2 effect

Table 3 (continued)

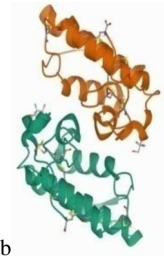
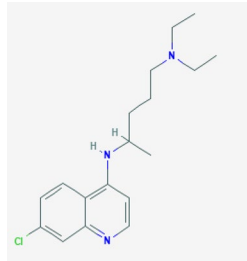
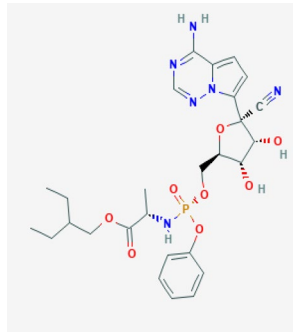
Coagulation pathways	C/anticoagulant and thrombolytic effects					
DENV	PLA2	*Bl*K-PLA$_2$; *(Bothrops leucurus)*[285]	 5TFV.pdb	May decrease viral RNA levels leading to reduce SARS-CoV-2 load and preventing virions' propagation	Drug candidates being repurposed as potential therapeutics for COVID-19 treatment	Structure
					Chloroquine It has diverse modes of action, including alteration of the acidic environment inside lysosomes and late endosomes, preventing endocytosis, exosome release and phagolysosomal fusion, and inhibition of the host cytokine storm [286]	
		*Bl*D-PLA$_2$ *(Bothrops leucurus)* [285]			Remdesivir Remdesivir, is a nucleoside prodrug or nucleotide analog It targets viral replication enzymes, due to its function as nucleoside analog during viral replication that result in deadly mutations [287] Remdesivir has good efficacy against a broad-spectrum of viruses including coronaviruses, SARS, MERS and CoVs	

Table 3 (continued)

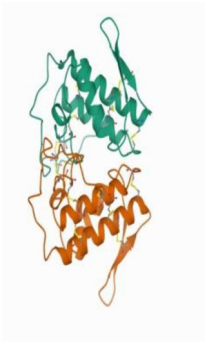
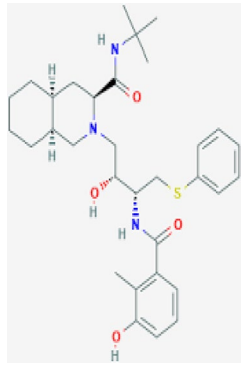
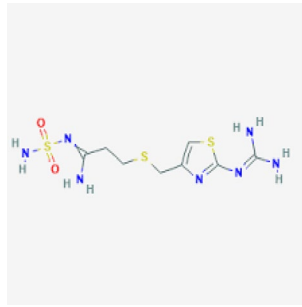
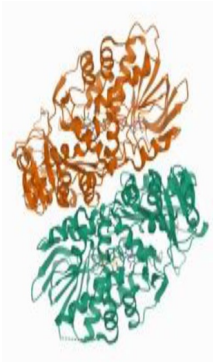
Coagulation pathways	C/anticoagulant and thrombolytic effects				
DENV, YFV	PLA_2-Cdt *Crotalus durissus terrificus* [288, 289]	1PP2.pdb 	Possible virus envelope cleavage and protein destabilization of SARS-CoV-2	Nelfinavir It is an anti-retroviral drug that selectively inhibits human immunodeficiency virus (HIV) protease Mechanistically, Nelfinavir prevents cleavage of gag-pol viral polyprotein that results in release of immature and non-infectious virions[290]. Previous results with SARS and MERS CoV have shown that Spike (S) glycoprotein is a major determinant of virus infectivity and immunogenicity	
HIV	PLA_2-Cdt *Crotalus durissus terrifics*[291],		Gag p24 processing inhibition of HIV, antiviral mechanism against SARS-CoV-2 needs to be investigated	Famotidine It is a competitive antagonist for histamine H2-receptor It acts as an inhibitor for gastric secretion. The preventive effect of famotidine on gastric lesions is attributable not only to suppression of acid secretion but to activation of gastric mucosal defensive mechanisms[292]	

Table 3 (continued)

Coagulation pathways	C/anticoagulant and thrombolytic effects			
DENV-3	LAAO	Bjar LAAO-I *Bothrops jararaca* [273]	4E0V.pdb 	Possivbly reduce infected cells
HIV-1		TSV-LAO *Trimeresurus stejnegeri* [293]		Syncytium formation inhibition and HIV-1 p24 antigen reduction; mechanism anti-SARS-CoV-2 to investigate
HIV	Non enzymatic peptides	Immunokine *from Naja kaouthia* (*Naja siamensis*) venom [294]		Possible mimicking the same mechanism as in anti-HIV via binding CCR5 and CXCR4 receptors

TXA2: thromboxaneA2, ADP: adenosine diphosphate, HIV-1 human immunodeficiency virus type1, MeV measles virus, HBV hepatitis B virus, HCV hepatitis C virus, SARS-CoV severe acute respiratory syndrome/coronavirus

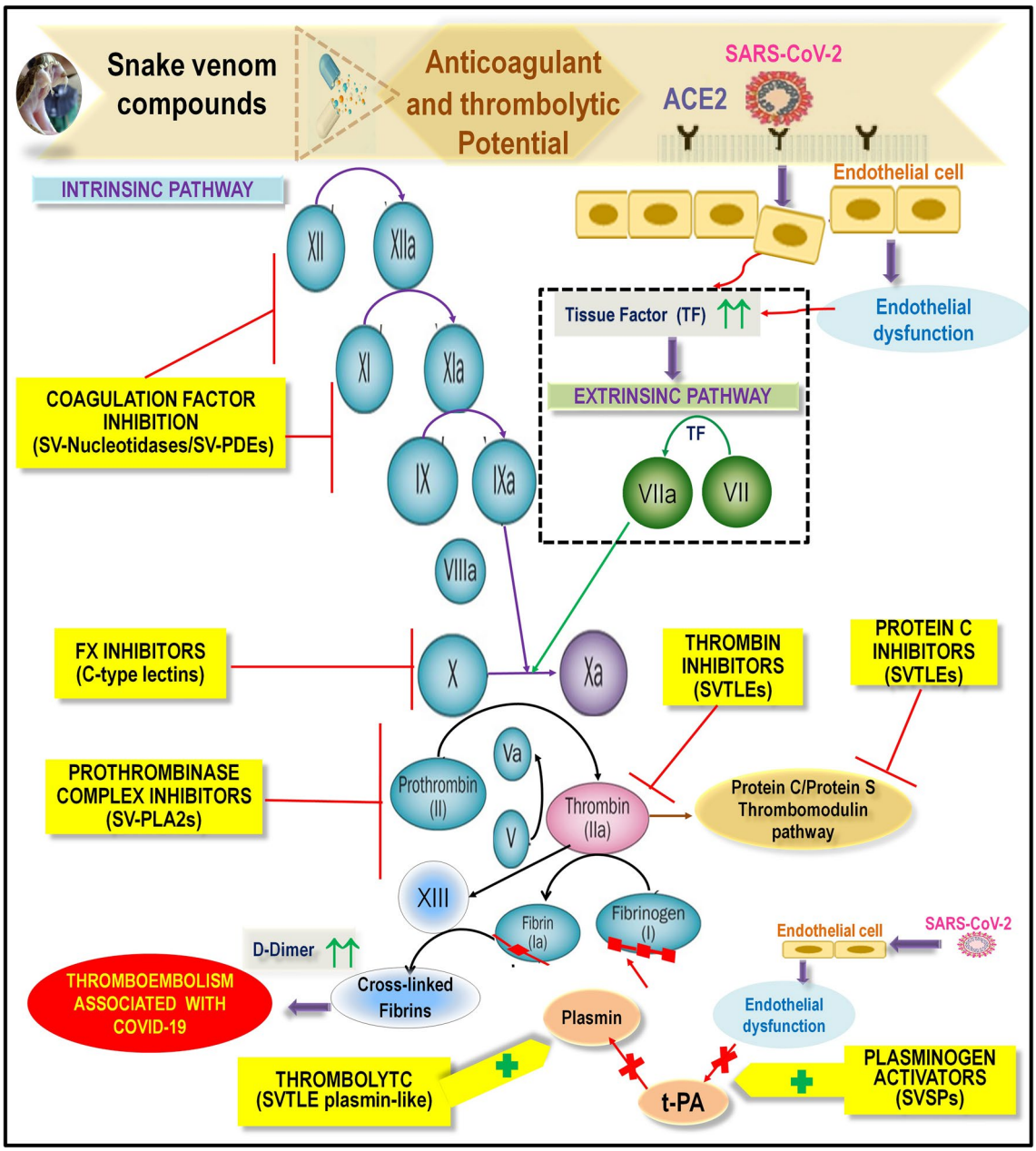


Fig. 7 Potential inhibitory effects of snake venom compounds on coagulopathy associated with COVID-19 and their anti-thrombotic and antiviral mechanism [226, 227]

9 Conclusion

This review focused on (i) the comparison of the hemostasis disorders induced by snake venoms with coagulopathy associated with COVID-19, both complications seem to be similar and share several common features; (ii) The use of investigational drugs isolated from snake venoms and the identification of their effective potential as biotherapeutics to treat diseases.

As snake venoms are well-known and the most investigated of all other animal venoms, their bio-compounds are gaining renewed interest as potential sources of new relevant pharmaceutical biotherapeutics and biodiagnostics for human pathologies. The specificity of snake venom proteins and peptides and their bioactivities to target cardiovascular and hemostatic processes make them as promising pharmacological agents. Several compounds derived from snake venoms could be potential candidates as therapeutic and diagnostic agents to COVID-19 pandemic. All of these

data, alongside current works into components of snake venoms, predict an exciting future for the likely use of snake venom derived-compounds in the field of drug discovery.

Acknowledgements The authors express their gratitude to Dr. Megdad-Lamraoui Amal (USTHB, Faculty of Biological Sciences; Laboratory of Cellular and Molecular Biology) for her kind help and assistance in formatting list of references according to the journal.

Author Contributions Both authors contributed equally to this work, designed the study, provided data and wrote the article.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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