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

Fatah Chérifi1 · Fatima Laraba-Djebari1

Accepted: 24 August 2021 / Published online: 9 September 2021
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 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.
Keywords  SARS-CoV-2 variants · COVID-19 · Snake venoms · Coagulopathy · Antiplatelet peptides · Antithrombotic compounds

Abbreviations

| Acronym | Description |
|---------|-------------|
| 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 |
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].
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.

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)

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
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 metalloprotease 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 raccoon 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 viral infection destructiveness. 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 A2 (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].

---

806 F. Chérifi, F. Laraba-Djebari
• 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*       | Fibrinogen          | aPTT, fibrinogen | [85]       |
|                        | Green bush viper           |                     |            |            |
| TLE                    | *Atheris chlorechis*       | Fibrinogen          | PT, aPTT, fibrinogen | [86]       |
| TLE                    | Western bushviper          | Fibrinogen          | PT, aPTT, fibrinogen, D-dimer | [87]       |
| TLE                    | *Atheris nitschei*         | Fibrinogen          | PT, aPTT, fibrinogen, D-dimer | [88, 89]   |
| TLE                    | *Cerastes cerastes*        | Fibrinogen, FV      | PT, aPTT, fibrinogen, D-dimer, factor V | [88, 89]   |
| TLE (cerastobin)       | *Cerastes vipers*          | Fibrinogen          | PT, aPTT, fibrinogen, D-dimer | [88]       |
|                        | Sahara sand viper          |                     |            |            |
|                        | *Proatheris superciliaris* | Fibrinogen          | PT, aPTT, fibrinogen, D-dimer | [90]       |
| TLE                    | Bitis arietans             | Fibrinogen          | Fibrinogen, PT, clotting factor studies | [91–93]    |
| TLE (Gabonase)         | *Bitis gabonica*           | Fibrinogen          | Fibrinogen, PT, clotting factor studies | [94]       |
| FII activators         | *Echis coloratus*          | Fibrinogen, ?, FII, FV, FVIII | Fibrinogen, FDP, PT | [95, 96]   |
|                        | Painted carpet viper       |                     |            |            |
| FII activators         | *Echis ocellatus*          | Fibrinogen, FII, FV, FVIII | fibrinogen, clotting factor studies | [97]       |
| FII activators         | West African carpet viper  | Fibrinogen, FII, FV, FVIII | Fibrinogen, PT, clotting factor studies | [98, 99]   |
| FII activators         | *Dispholidus typus*        | Fibrinogen          | PT, aPTT, fibrinogen, FDP | [100]      |
| SVMP*                  |                            |                     |            |            |
| B/Asia                 |                            |                     |            |            |
| FX, FV activators      | *Daboia russelii*          | Fibrinogen, FV, FX  | WBCT20, CT, fibrinogen, clotting factor studies | [101, 102] |
|                        | Russell’s viper            |                     |            |            |
| FX, FV activators      | *Daboia russelii siamensis*| Fibrinogen, FV, FX  | PT, non-clotting blood | [103]      |
|                        | Eastern Russell’s viper    |                     |            |            |
|                        | Siamese Russell’s viper    |                     |            |            |
| TLE                    | *Hypnale hypnale*          | Fibrinogen, FVIII   | PT, aPTT, clotting factor studies, D-Dimer | [104]      |
| FII activators         | *Echis carinatus*          | NR                  | PT         | [105]      |
|                        | Saw scaled viper           |                     |            |            |
| TLE                    | *Calloselasma rhodostoma*  | Fibrinogen          | Fibrinogen, FDP, clotting factor studies | [106]      |
| TLE                    | Malayan pit viper          | Fibrinogen          | Fibrinogen, FDP, fibrinopeptide A, plasminogen | [107]      |
| TLE                    | *Trimeresurus albolabris*  | Fibrinogen          | Fibrinogen, FDP, fibrinopeptide A, plasminogen | [108]      |
| TLE                    | White-lipped green pit viper| Fibrinogen          | Fibrinogen, FDP, fibrinopeptide A, plasminogen | [108]      |
Table 1 (continued)

| Region          | Species                        | Bioactive Components | Additional Notes                     | Reference |
|-----------------|--------------------------------|----------------------|--------------------------------------|-----------|
| B/Asia          | Large-eyed pitviper (green pitviper) | Trimeresurus stejnegeri | Bamboo pitviper, Chinese tree viper  |           |
| TLE, plasminogen activator |                      | Fibrinogen | Fibrinogen, FDP, AT-III | [109]      |
| ND              | Rhabdophis subminiatus (Red-necked keelback) | Fibrinogen | PT, aPTT, Fibrinogen, FDP |           |
| ND              | Rhabdophis tigrinus (Tiger keelback) | Fibrinogen | PT, aPTT, Fibrinogen, FDP | [110]      |
| C/Australia     | FII activators                | Pseudonaja spp.      | Brown snake                         |           |
|                 | Notechis scutatus             | Fibrinogen, FII, FV, FVIII | PT, aPTT, Fibrinogen, FDP | [75]      |
|                 | Tiger snake                   | Fibrinogen, FII, FV, FVIII | PT, aPTT, clotting factor studies, D-dimer |           |
|                 | Tropidechis carinatus         | Fibrinogen, FII, FV, FVIII | PT, aPTT, clotting factor studies, D-dimer |           |
|                 | Rough-scaled snake            | Fibrinogen, FII, FV, FVIII | PT, aPTT, D-dimer, FDP | [113]      |
|                 | Hoplocephalus spp.            | Fibrinogen, FII, FV, FVIII | PT, aPTT, clotting factor studies, D-dimer |           |
|                 | 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       | Western diamondback rattlesnake | Fibrinogen | PT, aPTT, Fibrinogen | [115]      |
|                 | TLE                            | Crotalus adamanteus  | Fibrinogen, D-dimer (normal) | PT, aPTT, fibrinogen, D-dimer, FDP, antiplasmin III | [116]      |
|                 | TLE                            | Crotalus molossus molossus | Black-tailed rattlesnake | Fibrinogen | PT, fibrinogen, FDP | [117]      |
|                 | TLE                            | Crotalus horridus    | Timber rattlesnake | Fibrinogen | Fibrinogen, FDP | [118]      |
|                 | TLE                            | Crotalus helleri     | Southern Pacific rattlesnake | Fibrinogen | PT, fibrinogen | [119]      |
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 α3β1 [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. 3A). 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
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-thromboembolic 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 hyper-coagulability 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].

---

**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)
- 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 vasodilation and release of tPA from ECs as do BBPs from snake venoms [78, 133, 143].

Several 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 IPA 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 hemo-stasis related to a hyperinflammatory profile that promotes endothelial dysfunction and induces a prothrombotic state. During disease, clots are formed through a thrombo-inflamma-tion process involving thrombocytes, factors of coagulation and some effectors of innate immune system (macrophages, polynuclear neutrophils and the complement), [152, 153].

Many associated pathological events occurred simultaneously when ACE2 is inhibited due to SARS-CoV2/ACE-2 receptor attachment leading to an uncontrolled and widespread immuno-thrombosis 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 inhibi-tor (TFPI) and the protein C system) and inactivated fibrino-lysis 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-inflamm-atory 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 anti-coagulants [160]. Otherwise, the increased procoagu-lants combined to decreased anticoagulants, preventing thrombolysis in the broad interchange between ECs, platelets, complement system, macrophages, polynu-clear 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 hyperinflam-mation through cytokine storm.

The IL-6 is associated with severity in COVID-19 patho-genesis; 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 recep-tor 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, Bhatla 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 infectional 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].
When activated, the platelet changes its 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 underlining 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).
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 that inhibit platelet aggregation as well as conventional antiplatelet drugs [23, 177–179].
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 Millenium 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 coronary syndrome) and prevented deadly heart attack in vulnerable patients [17, 189]. Eptifibatide is a GPIIb/IIIa 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 |
|--------------------------|--------------------|---------------------------------|------------------|---------------------------------|
| **A/Approved drugs derived from snake venoms as therapeutics** | | | | |
| Captopril® [181–184] | Bothrops jararaca | C9H15NO3S | 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 | C22H36N2O5S | 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 | C35H49N11O9S2 | Treatment of patients with acute coronary 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 | | | - 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 | | | - 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** | *Pseudonaja textilis* | Anti-fibrinolytic drug | Could be useful to control bleeding following anticoagulation therapy |
| [193] | | Use for reducing blood loss associated with complex surgeries | |
| **Hempatch** | *Pseudonaja textilis* | It was translated into novel therapeutics to control bleeding | Could be useful to control bleeding following anticoagulation therapy |
| [184, 193] | | 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 | |
| **Reptilase®** | *Bothrops atrox* and *Bothrops moojeni* | To measure fibrinogen levels and blood coagulation capability through the in vitro clotting time | Fibrinogen level testing for adequate and early management of individual with COVID-19 |
| (Batroxobin) | | - Used also to detect antithrombin activity | |
| [194, 195] | | | |
| **Pefakit®** | *Daboia russelii* | Used to identify factor V levels in plasma | 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 |
| (RVV-V) | | Used in assays for the diagnosis of resistance to activated protein C, which does not cleaves factors Va and VIIIa | |
| [195–197] | | Used to the diagnosis of lupus anticoagulant | |
| **Stypven®** | *Daboia russelii* | Platelet aggregation by increasing the affinity between the receptor GP Ibα and von Willebrand factor | Identification of von Willebrand factor deficiency or activation during coagulopathy linked to COVID-19 |
| (RVV-X) | *Echis carinatus* | | |
| [82, 195, 198] | | | |
| **Ecarin** | *Bothrops jararaca* | Platelet aggregation by increasing the affinity between the receptor GP Ibα and von Willebrand factor | Direct testing of thromboembolism), linked to deep vein thrombosis or pulmonary embolism associated with COVID-19 |
| [195, 199] | | | |
| **Botrocetin®** | *Agkistrodon contortrix contortrix* | Used to quantify protein S and C levels by prolongation of the activated partial thromboplastin time (aPTT) | |
| (Venom coagglutinin) | | Investigation of the cause of a blood clot (thromboembolism), linked to deep vein thrombosis or pulmonary embolism | |
| [195, 200] | | | |
| **Protac®** | *Mamba snake venoms* | Studies of novel treatments for blood pressure disorders (MTα) | Diagnosis of both COVID-19 complication; blood pressure disorders (MTα) blood coagulation disorders before and after treatment |
| [200] | | blood coagulation disorders (KT-6.93) | |
integrons 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 bio-diagnostics for three decades (Table 2B).

- Textilin-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 russelli 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® and Pefaki®, 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
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 coagulation such as FⅩa, 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, 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 αⅡbβ3 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].
| Virus and molecular targets | Mechanism of action of snake venom compounds | Conventional drugs |
|-----------------------------|---------------------------------------------|-------------------|
| Platelet receptor activators | A/Indirect antiplatelet effects | |
| von Willebrand Factor (vWF) | C-type lectins | |
| | Botroce-tin [177], bitisicetin [178] | |
| | 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’-NTase [229]; Cc-5’NTase [23] | |
| | 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 pathogenesis | |
| | 5H7W.pdb | |
| | Thienspyridines | |
| | 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 | Drug name | Structure | Side effects and drug resistance |
| ADP | PDEs/ADPase/RNase | DR-PDE of Daboa 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], Ce-PDE of Cerastes cerastes [228] | Snake venom RNases disturb genomic RNA of SARS-CoV-2 exhibiting antiviral action by affecting viral RNA replication and translation | 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] | Possibly binds to platelet P2Y1 receptor Inhibit platelet activation mediated through P2Y12 receptor | 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], flavordin and kistrin [240], CCSV-MPase [74], Disintegrin-Cc [241], Cerastategrin [202] |
| | **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** |
| | **Dendroaspis jamesoni kaimosae** (also named mambin; UniProt KB P28375) [242], S5C1 (UniProt KB number P01413) **Dendroaspis jamesoni kaimosae** [243], Thrombostatin, (UniProtKB P81946), **Dendroaspis angusticeps** |
| | **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] **Antifabatide** (trade name of agkicacetin [248]) |
| | **GPIb receptor of vWF, an effective target for inhibition of platelet adhesion in antithrombotic therapy** |
| | **Monoclonal antibodies** |
| | **Aptamers** |
| | **GPIbα blockade by antifabatide treatment could be useful in ischemic stroke through inhibition of thrombosis** |
Table 3 (continued)

| Platelet receptors | B/direct antiplatelet effects |
|--------------------|------------------------------|
| αβ2/β1 (ITGa2/ITGb1) | Disintegrin like-domain of SVMPs | Trigramin [249–251], bitistatin [252, 253] | Platelet inhibition via interactions with αβ2/β1 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] Atroxysin-III [261] | 1WNL.pdb | Cleavage of glycoprotein VI (GPVI) into a soluble ~ 55-kDa fragment (sGPVI). Thereby, inhibition 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) | Bothrojacin[262], Cc-Lec [24] | IIXX.pdb | Anticoagulant function of great therapeutic value, related to 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 thy 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.**

| Coagulation pathways | C/anticoagulant and thrombolytic effects |  |
|----------------------|---------------------------------------|---|
| Fibrinogen           | SVTLEs (Fibrinogen-ases)              | 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     | SVTLEs (Fibrinases)                       |  |
| Thrombin and FXa     | BjussuSP-I [273], agacutin [274], purpurase [275] and pictobin [276], Crotalase [277], gabonase [277], cerastobin [278] Afaâcytin [8] Fibrolase [279] | No stimulation 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              | Enoxaparin sodium                        | 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] |
Table 3 (continued)

Coagulation pathways C/anticoagulant and thrombolytic effects

| Fibrinogen | Three-finger toxins | Exactin (UniProtKB number P0DQH2, Hemachatus haemachatus) [281] Ringhalexin (UniProtKB number C0HJT, Hemachatus haemachatus) [282] Najalexin UniProtKB number Q5W717 Naja atra [283] Ophiolatin UniProtKB number V8N9N7 Ophiophagus hannah [283] Hemexin AB complex UniProtKB number P0DQH3, P0DQH4, Hemachatus haemachatus [284] | 3VTS.pdb | Binding toand inhibition of FVIIa-TF interaction without the need for substrate (FX) Attenuation of the initiation of coagulation Blockade of extrinsic coagulation pathway Hyperactivated resulting in endothelial dysfunction associated with COVID-19, leading to thromboembolic disorders and lung embolism |
|---|---|---|---|---|

TAR-GETED VIRUS D/Antiviral effect E/Anti-SARS-CoV-2 effect
### Table 3 (continued)

| Coagulation pathways | C/anticoagulant and thrombolytic effects | Drug candidates being repurposed as potential therapeutics for COVID-19 treatment | Structure |
|----------------------|------------------------------------------|-------------------------------------------------------------------------------|-----------|
| **DENV PLA2** | *BiK-PLA*₂ (*Bothrops leucurus*) [285] | May decrease viral RNA levels leading to reduce SARS-CoV-2 load and preventing virions’ propagation | | 5TFV.pdb |
| **B/D-PLA**₃ (*Bothrops leucurus*) [285] | | 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] | | |
| | 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

| Virus       | PLA2-Cdt *Crotalus durissus terrificus* [288, 289] | Possible virus envelope cleavage and protein destabilization of SARS-CoV-2 | Nelfinavir | Gag p24 processing inhibition of HIV, antiviral mechanism against SARS-CoV-2 | Famotidine |
|-------------|--------------------------------------------------|--------------------------------------------------------------------------|------------|--------------------------------------------------------------------------------|------------|
| DENV, YFV  | IPP2.pdb                                         |                                                                          |            | It is an anti-retroviral drug that selectively inhibits human immunodeficiency virus (HIV) protease |            |
| HIV         | PLA2-Cdt *Crotalus durissus terrificus* [291],   |                                                                          |            | 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 |            |
|             |                                                  |                                                                          |            | Farnotidine 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] | Possibly 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: thromboxane A2, ADP: adenosine diphosphate, HIV-1 human immunodeficiency virus type 1, MeV measles virus, HBV hepatitis B virus, HCV hepatitis C virus, SARS-CoV severe acute respiratory syndrome/coronavirus
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.

References

1. Piva S, Filippini M, Turla F, Cattaneo S, Margola A, De Fulviis S, Nardiello I, Beretta A, Ferrari L, Trosta R, Erbici G (2020) Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy. J Crit Care. 58:29–33
2. Touret F, de Lamballerie X (2020) Of chloroquine and COVID-19. Antiviral Res 177:104762
3. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C (2020) In vitro anti-viral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis
4. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, Götte M (2020) Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem 295:6785–6797. https://doi.org/10.1074/jbc.RA120.013679
5. Malin JJ, Suárez I, Priesner V, Fiitkenhauer G, Rybniker J (2020) Remdesivir against COVID-19 and other viral diseases. Clin Microbiol Rev. 34(1):e00162-20. https://doi.org/10.1128/CMR.00162-20
6. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z (2020) Anti-coagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18(5):1094–1099
7. Vinayagam S, Sattu K (2020) SARS-CoV-2 and coagulation disorders in different organs. Life Sci 118431
8. Suresh PS. Curcumin and Coagulopathy in the COVID19 Era. Indian J Clin Biochem. 2020 Jul 15;35(4):1–2. doi: https://doi.org/10.1007/s12291-020-00914-5.
9. Fatima L, Fatah C (2014) Pathophysiological and pharmacological effects of snake venom components: molecular targets. J Clin Toxicol 4 (190):2161–0495.2190
10. Laraba-Djebbari F, Martin-Eauclaire MF, Mauro G, Marchot P (1995) Afaâcytin, an αβ-fibrinogenase from Cerastes cerastes (Horned Viper) Venom, activates purified factor X and induces serotonin release from human blood platelets. Eur J Biochem 233(3):756–765
11. Rashidi R, Valokola MG, Rad SZK, Etemad L, Roohbakhsh A (2018) Antiplatelet properties of snake venoms: a mini review. Toxin Reviews
12. Torres A, Dantas R, Menezes R, Toyama M, Oliveira M, Nogueira N, Oliveira M, Monteiro H, Martins A (2010) Antimicrobial activity of an L-amino acid oxidase isolated from Bothrops leucurus snake venom. J Venomous Anim Toxins Incl Trop Dis 16(4):614–622
13. Kuna E, Bocian A, Hus KK, Petrilla V, Petrillova M, Legath J, Lewinska A, Wnuk M (2020) Evaluation of antifungal activity of Naja pallida and Naja mossambica venoms against three Candida species. Toxins 12(8):500
14. Cisotto P, de Avila RM, Coelho EA, Oliveira J, Diniz CG, Farías LM et al (2009) Antigenic, microbicidal and antiparasitic properties of an L-amino acid oxidase isolated from Bothrops jararaca snake venom. Toxicon 53(3):330–341
15. Ferreira SH, Bartelt DC, Greene LJ (1970) Isolation of bradykinin-potentiating peptides from Bothrops jararaca venom. Biochemistry 9(13):2583–2593
16. Tu AT, Wiley J (1977) Venoms: chemistry and molecular biology
17. Peerlinck K, De Lepeleire I, Goldberg M, Farrell D, Barrett J, Hand E, Panebianco D, Deckmyn H, Vermyn J, Arnout J (1993) MK-383 (L-700,462), a selective nonpeptide platelet glycoprotein Ib/IIa antagonist, is active in man. Circulation 88(4):1512–1517
18. Fanard D, Lambeau G, Valentin E, Lefebvre J-C, Lazdunski M, Doglio A (1999) Secreted phospholipases A 2, a new class of HIV inhibitors that block virus entry into host cells. J Clin Investig 104(5):611–618
19. Hutton R, Warrell D (1993) Action of snake venom components on the haemostatic system. Blood Rev 7(3):176–189
20. Cherifi F, Namane A, Laraba-Djebbari F (2014) Isolation, functional characterization and proteomic identification of CC2-PLA 2 from Cerastes cerastes venom: a basic platelet-aggregation-inhibiting factor. Protein J 33(1):61–74
21. Slagboom J, Kool J, Harrison RA, Casewell NR (2017) Haemotoxico snake venoms: their functional activity, impact on snakebite victims and pharmaceutical promise. Br J Haematol 177(6):947–959
22. Tosoulis T, Isbister GK (2017) A review and database of snake venom proteomes. Toxins 9(9):290
23. Saoud S, Cherifi F, Benhassine T, Laraba-Djebbari F (2017) Purification and characterization of a platelet aggregation inhibitor and anticoagulant of Ce 5 NTase, Cd 73-like, from Cerastes cerastes venom. J Biochem Mol Toxicol 31 (5):1885
24. Samah S, Fatah C, Jean-Marc B, Safia K-T, Fatima L-D (2017) Purification and characterization of Cc-Lec, C-type lactose-binding lectin: a platelet aggregation and blood-clotting inhibitor from Cerastes cerastes venom. Int J Biol Macromol 102:336–350
25. Munawar A, Ali SA, Akrem A, Betzel C (2018) Snake venom peptides: tools of bioscience. Toxins 10(11):474
26. Labo N, Ohnuki H, Tosato G (2020) Vasculopathy and coagulopathy associated with SARS-CoV-2 infection. Cells 9(7):1583
27. Maduwage K, Isbister GK (2014) Current treatment for venom-induced consumption coagulopathy resulting from snakebite. PLoS Negl Trop Dis 8(10):e3220
28. Mohamed Abul Aziz T, Soares AG, Stockand JD (2019) Snake venoms in drug discovery: valuable therapeutic tools for life saving. Toxins 11(10):564
29. Gempeler-Messina P, Volz K, Bühler B, Müller C (2001) Protein C activators from snake venoms and their diagnostic use. Patho-physiol Haemost Thromb 31(3–6):266–272
30. Serrano SM (2013) The long road of research on snake venom serine proteinases. Toxiconomy 62:19–26
of the interactions of the integrin αIIbβ3 with immobilized glycoprotein ligands by snake-venom RGD (Arg-Gly-Asp) proteins. Evidence supporting a functional role for the amino acid residues flanking the tripeptide RGD in determining the inhibitory properties of snake-venom RGD proteins. Biochem J 304 (3):929–936

32. Silva MB, Schattner M, Ramos CR, Junqueira-de-Azevedo IL, Guarnieri MC, Laarazi MA, Sampaio CA, Pozner RG, Ventura GS, Ho PL (2003) A prothrombin activator from Bothrops erythromelas (jararaca-da-seca) snake venom: characterization and molecular cloning. Biochem J 369(1):129–139

33. Guo YR, Cao QD, Hong ZS et al (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. Mil Med Res 7(1):11. https://doi.org/10.1186/s40779-020-00240-0

34. https://www.who.int/health-topics/coronavirus#tab=tab_3

35. Drosten C, Gündüner S, Preiser W, Van Der Werf S, Brodt H-R, Becker S, Rabenau H, Panning M, Kolesnikova L, Fouchier RA (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 348(20):1967–1976

36. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery V-R, Myers JF, Nicholson JG, Shope RE, Specter SE, Rollin PE, Roehrig JT, Rota PA, Moncef S, Nichol ST, Groll AJ (2003) A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 348(18):1945–1950

37. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA (2012) Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 367(19):1814–1820

38. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R (2020) A novel coronavirus from patients with pneumonia in China, 2019. New England journal of medicine

39. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497–506

40. World Health Organization (2020) Flammé de maladie à coronavirus 2019 (COVID-19). Search. https://www.who.int/. Accessed 22 Nov 2020

41. Shah SH, Moore E, Robertson C, McMenamin J, Katikireddi SV, Simpson CR et al (2021) Predicted COVID-19 positive cases, hospitalisations, and deaths associated with the Delta variant of concern, June–July, 2021. Lancet Digit Health 2021 Published Online August 9, 2021 https://doi.org/10.1016/S2589-7500(21)00175-8

42. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intens Care Med 46(4):586–590. https://doi.org/10.1007/s00134-020-05985-9

43. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ (2000) A human homolog of angiotensin-converting enzyme cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem 275(43):33238–33243

44. Hu B, Zeng L-P, Yang X-L, Ge X-Y, Zhang W, Li B, Xie J-Z, Shen X-R, Zhang Y-Z, Wang N (2017) Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathogens 13(11):e1006698

45. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, Wang H, Crameri G, Hu Z, Zhang H (2005) Bats are natural reservoirs of SARS-like coronaviruses. Science 310(5748):676–679

46. Wang M, Yan M, Xu H, Liang W, Kan B, Zheng B, Chen H, Zheng H, Xu Y, Zhang E (2005) SARS-CoV infection in a restaurant from palm civet. Emerg Infect Dis 11(12):1860

47. Liu DX, Liang JQ, Fung TS (2020) Human coronavirus-229E, OC43,-NL63, and-HKU1. Reference Module Life Sci. B978-0

48. Ke Z, Oton J, Qu K et al (2020) Structures and distributions of SARS-CoV-2 spike proteins on intact virions. Nature 588:498–504. https://doi.org/10.1038/s41586-020-2665-2

49. Spiga O, Bernini A, Ciutti A, Chelliini S, Menciassi N, Finetti F, Causarono V, Anselmi F, Frisch F, Niccolai N (2003) Molecular modelling of S1 and S2 subunits of SARS coronavirus spike glycoprotein. Biochem Biophys Res Commun 310(1):78–83

50. Vkovski P, Kratzel A, Steiner S, Stalder H, Theil V (2021) Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol 19(3):155–70

51. V'kovski P, Kratzel A, Stalder H, Theil V (2021) Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol 19(3):155–70

52. Sarma P, Shekhar N, Prajapati M, Avti P, Kaur H, Kumar S, Singh S, Kumar H, Prakash A, Dhibar DP, Medhi B (2021) In-silico homology assisted identification of inhibitor of RNA binding against 2019-n-CoV N-protein (N terminal domain). J Biomol Struct Dyn 39(8):2724–32

53. Ruch TR, Machamer CE (2012) The coronavirus E protein: assembly and beyond. Viruses 4(3):363–382

54. Schoeman D, Fielding BC (2019) Coronavirus envelope protein: current knowledge. Virol J 16(1):1–22

55. Ciulla MM (2020) SARS-CoV-2 downregulation of ACE2 and pleiotropic effects of ACEI/ARBs. Hypertens Res 43(9):985–986

56. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ, van der Hoeven H (2020) Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife 9:e57555

57. Zambelli V, Bellani G, Borsa R, Pozzi F, Grassi A, Scanziani M, Castiglioni V, Masson S, Decio A, Lafey JF (2015) Angiotensin-(1–7) improves oxygenation, while reducing cellular infiltrate and fibrosis in experimental Acute Respiratory Distress Syndrome. Intens Care Med Exp 3(1):1–17

58. Kuba K, Imai Y, Rao S, Jiang C, Penninger JM (2006) Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. J Mol Med 84(10):814–820

59. Green SJ (2020) Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. Microbes Infect 22(4):149

60. Ozdemir B, Yazici A (2020) Could the decrease in the endothelial nitric oxide (NO) production and NO bioavailability be the crucial cause of COVID-19 related deaths? Med Hypotheses 144:109970

61. Horby P, Huntley C, Davies N, Edmunds J, Ferguson N, Medley GJ,遍布全网; Haidar G (2021) Duprex WP (2021) Recurrent infection case confirmed in Brazil, 2020. New Variant Strain of SARS-CoV-2 Identified in Travelers from Brazil [Press release]. Retrieved from https://www.niid.go.jp/niid/en/2019-ncov-e/10108-covid19-33-en.html external icon. Accessed 18 Feb 2020

62. National Institute of Infectious Diseases J (2021) Brief report: New Variant Strain of SARS-CoV-2 Identified in Travelers from Brazil [Press release]. Retrieved from https://www.niid.go.jp/niid/en/2019-ncov-e/10108-covid19-33-en.html external icon. Accessed 18 Feb 2020

63. Resende PC, Bezerra-JF, de Vasconcelos RHT, Arantes I, Appolinario L, Mendoza AC, Paixao AC, Rodrigues ACD, Silva T, Rocha AS Spike E484K mutation in the first SARS-CoV-2 recombination case confirmed in Brazil, 2020.

64. Zhov B, Thao TTN, Hoffmann D, Taddeo A, Ebert N, Labrousse A, Pohlmann A, King J, Portmann J, Halwe N (2020) SARS-CoV-2 spike D614G variant confers enhanced replication and transmissibility. bioRxiv

65. McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy AE, Bain WG, Haidar G (2021) Duprex WP (2021) Recurrent infection case confirmed in Brazil, 2020.
transmission of a SARS-CoV-2 Spike deletion ΔH69/V70. bioRxiv

67. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA (2017) Snakebite envenoming. Nat Rev Dis Primers 3(1):1–21

68. World Health organization (2018) Neglected tropical diseases. http://www.who.int/neglected_diseases/en/. Accessed 2019

69. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena Harrison RA, Casewell NR, Ainsworth SA, Lalloo DG (2019) Zelanis A, Tashima AK (2014) Unraveling snake venom com-

70. Harrison RA, Gutiérrez JM (2016) Priority actions and progress to substantially and sustainably reduce the mortality, morbidity and socioeconomic burden of tropical snakebite. Toxins 8(12):351

71. Harrison RA, Casewell NR, Ainsworth SA, Laloo DG (2019) The time is now: a call for action to translate recent momentum on tackling tropical snakebite into sustained benefit for victims. Trans R Soc Trop Med Hyg 113(12):835–838

72. Zelans A, Tashima AK (2014) Unraveling snake venom complexity with ‘omics’ approaches: challenges and perspectives. Toxiconomy 87:131–134

73. Kini RM, Koh CY (2016) Metalloproteases affecting blood coagulation, fibrinolysis and platelet aggregation from snake venoms: Definition and nomenclature of interaction sites. Toxins 8(10):284

74. Chérif R, Rousseau J-C, Namane A, Laraba-Djebari F (2010) CCSV-MPase, a novel procoagulant metalloproteinase from Cerastes cerastes venom: purification, biochemical characterization and protein identification. Protein J 29(7):466–474

75. Isbister GK, Scorgie F, O’leary M, Seldon M, Brown SG, Lincz L, INVESTIGATORS A (2010) Factor deficiencies in venom-induced consumption coagulopathy resulting from Australian elapid envenomation: Australian Snakebite Project (ASP-10). J Thromb Haemost 8(11):2504–2513

76. Gutiérrez JM, Escalante T, Rucavado A, Herrera C (2016) Hemorrhage caused by snake venom metalloproteinases: a journey of discovery and understanding. Toxins 8(4):93

77. Mosquera A, Idrovo LA, Tafur A, Del Brutto OH (2003) Stroke induced consumption coagulopathy resulting from Australian elapid envenomation. Australian Snakebite Project (ASP-10). J Thromb Haemost 8(11):2504–2513

78. Phillips DJ, Swenson S, Francis S, Markland J, Mackessy S (2005) Snake venom fibrin (ogen) activators of factor X: an overview. Pathophysiol Haemost Thromb 31(3–6):225–233

79. Swenson S, Markland F Jr (2005) Snake venom fibrin (ogen)olytic enzymes. Toxicology 45(8):1021–1039

80. Sanchez EF, Felicori LF, Chavez-Olortegui C, Magalhaes HB, Hermogenes AL, Diniz MV, LM de Junqueira-de-Azevedo L, Magalhaes A, Richardson M (2006) Biochemical characterization and molecular cloning of a plasminogen activator proteinase (LV-PA) from bushmaster snake venom. Biochim Biophys Acta BBA 1760 (12):1762–1771

81. Mebs D, Holada K, Simák J, Vanková H, Müller D, Schoennemann H, Lange H, Herrmann H (1998) Severe coagulopathy after a bite of a green bush viper (Atheris squamiger): case report and biochemical analysis of the venom. Toxiconomy 36(10):1333–1340

82. Top L, Tulleken J, Litgenberg J, Meertens J, Van der Werf T, Zijlstra J (2006) Serious envenomation after a snakebite by a Western bush viper (Atheris chlorechis) in the Netherlands: a case report. Neth J Med 64(5):153–156

83. Hatten BW, Bueso A, French LK, Hendrickson RG, Horowitz BZ (2013) Envenomation by the great lakes bush viper (Atheris nitschki). Clin Toxicol 51(2):114–116

84. Lifshitz M, Kastel H, Harman-Bohem I (2002) A novel high molecular weight fibrinogenase from the venom of Bitis arietans. Biochim Biophys Act ABA 1427(1):82–91

85. Warrell D, Ormerod L, Davidson NM (1975) Bites by puff-adder (Bitis arietans) envenomation with coagulopathy. J Toxicol Clin Toxicol 40(7):911–918

86. McNally T, Conway G, Jackson L, Theakston RDG, Marsh N, Warrell D, Young L, Mackie I, Machin S (1993) Accidental envenomation by a Gaboon viper (Bitis gabonica): the haemostatic disturbances observed and investigation of in vitro haemostatic properties of whole venom. Trans R Soc Trop Med Hyg 87(1):66–70

87. Portah A, Gilon D, Schulchnyska-Castel H, Shalev O, Keynan A, Benbassat J (1992) Risk indicators after envenomation in humans by Echis coloratus (mid-east saw scaled vipers). Toxiconomy 30(1):25–32

88. Mann G (1978) Echis colorata bites in Israel: an evaluation of specific antiserum use on the base of 21 cases of snake bite. Toxicol Eur Res 1(6):365–369

89. Warrell D, Ormerod L, Davidson NM, Greenwood B, Ormerod L, Pope HM, Watkins BJ, Prentice C (1977) Poisoning by bites of the saw-scaled or carpet viper (Echis carinatus) in Nigeria. QJM 46(1):33–62

90. Mion G, Larreché S, Benois A, Petitjeans F, Puidupin M (2013) Hemostasis dynamics during coagulopathy resulting from Echis coloratus (mid-east saw scaled vipers). Toxiconomy 76:103–109

91. Gillissen A, Theakston RDG, Barth J, May B, Krieg M, Warrell DA (1994) Neurotoxicity, haemostatic disturbances and haemolytic anaemia after a bite by a Tunisian saw-scaled or carpet viper (Echis ‘pyramidum’-complex): failure of antivenom treatment. Toxiconomy 32(8):937–944

92. Atichison J (1990) Boomsland bite—diagnosis and management. A report of 2 cases. S Afr Med J 78(1):39–42

93. Phillips RE, Theakston RDG, Warrell DA, Galgedara Y, Abeysekera D, Disnayakaya P, Hutton RA, Aloysius DJ (1988) Paralysis, rhabdomyolysis and haemolysis caused by bites of Russell’s viper (Vipera russelli pulchella) in Sri Lanka: failure of Indian (Haffkine) antivenom. QJM 68(3–4):691–715

94. Isbister G, Maduwage K, Shahmy S, Mohamed F, Abeyninghe C, Karunathilake H, Ariaratnam C, Buckley N (2013) Diagnostic 20-min whole blood clotting test in Russell’s vipers envenoming delays antivenom administration. QJM 106(10):925–932
103. Than T, Hutton R, Lwin M, Han KE, Soe S, Sway TN, Phillips R, Warrell D (1988) Haemostatic disturbances in patients bitten by Russell’s viper (Vipera russelli siamensis) in Burma. Br J Haematol 69(4):513–520

104. Maduwa K, Scorgie F, Silva A, Shahmy S, Mohamed F, Abeyesinghe C, Karunathilake H, Lincz L, Gnananathasan CA, Isbister G (2013) Hum-pit viper (Hypnem hypipalae) envenoming causes mild coagulopathy with incomplete clotting factor consumption. Clin Toxicol 51(7):527–531

105. Kularatne S, Sivansuthan S, Medagedara S, Maduwa K, de Silva A (2011) Revisiting saw-scaled viper (Echis carinatus) bites in the Jaffna Peninsula of Sri Lanka: distribution, epidemiology and clinical manifestations. Trans R Soc Trop Med Hyg 105(10):591–597

106. Warrell DA, Looareesuwan S, Theakston RDG, Phillips RE, Kularatne S, Sivansuthan S, Medagedara S, Maduwage K, de Silva SM, Monteiro MRdCdC, Fan HW, Cardoso P, Karbwang J, Ho M, Hutton RA (1986) Randomized comparative trial of three monospecific antivenoms for bites by the Malayan pit viper (Calloselasma rhodostoma) in southern Thailand: clinical and laboratory correlations. Am J Trop Med Hyg 35(6):1235–1247

107. Hutton R, Looareesuwan S, Ho M, Silamut K, Chanthavich P, Karbwang J, Supanaranond W, Vejcho S, Muanpasith P, Hutton RA (1985) Thrombin-generation syndrome. J Med Toxicol 4(3):180–183

108. Rojnuckarin P, Intragumtornchai T, Sattapiboon R, Muanpasith P, Hutton R, Looareesuwan S, Ho M, Silamut K, Chanthavanich P, Viravan C, Supanaranond W, Vejcho S, Muanpasith P, Medagearra S, Maduwage K, de Silva SM (2010) Covid-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 17(9):543–558

109. Li Q-B, Huang G-W, Kinjoh K, Nakamura M, Kosugi T (2001) Haemostatic disturbances in patients bitten by Russell’s viper (Vipera russelli siamensis) in Burma. Br J Haematol 69(4):513–520

110. Hasiba U, Rosenbach LM, Rockwell D, Lewis JH (1975) DIC-like syndrome after envenomation by the snake, Crotalus horridus horridus. N Engl J Med 292(10):505–507

111. Bush SP, Green SM, Moynihan JA, Hayes WK, Cardwell MD (2002) Crotalidae polyclonal immune Fab (ovine) antivenom is efficacious for envenomations by Southern Pacific rattlesnakes (Crotalus helleri). Ann Emerg Med 40(6):619–624

112. Boels D, Hamel JF, Deguigne MB, Harry P (2012) European viper envenomings: Assessment of Vipera™ and other symptomatic treatments. Clin Toxicol 50(3):189–196

113. Li Q-B, Huang G-W, Kinjoh K, Nakamura M, Kosugi T (2001) Hematological studies on DIC-like findings observed in patients with snakebite in south China. Toxicology 159(7):943–948

114. Nagai T, Sato Y, Hirasawa K, Honda A (1992) Thrombocytopenia and platelet hypoaggregability in children with rattlesnake bite. Clin Pediatr 31(2):149–154

115. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

116. Murakami MT, Arni RK (2005) Thrombomodulin-independent activation of protein C and specificity of heparinically active snake venom serine proteinases crystal structures of native and inhibited Agkistrodon contortrix contortrix protein c activator. J Biol Chem 280(47):39309–39315

117. Yip J, Shen Y, Berndt MC, Andrews RK (2005) Primary platelet adhesion receptors. IUBMB Life 57(2):103–108

118. Kini RM (2006) Anticoagulant proteins from snake venoms: structure, function and mechanism. Biochem J 397(3):377–387

119. Kang TS, Georgieva D, Genov N, Murakami MT, Sinha M, Kumar RP, Kaur P, Kumar S, Dey S, Sharma S (2011) Enzymatic toxins from snake venom: structural characterization and mechanism of catalysis. FEBS J 278(23):4544–4576

120. Boels D, Hamel JF, Deguigne MB, Harry P (2012) European viper envenomings: Assessment of Vipera™ and other symptomatic treatments. Clin Toxicol 50(3):189–196

121. Boels D, Hamel JF, Deguigne MB, Harry P (2012) European viper envenomings: Assessment of Vipera™ and other symptomatic treatments. Clin Toxicol 50(3):189–196

122. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

123. Camargo AC, Ianzer D, Guerreiro JR, Serrano SM (2012) Bradypnea in patients bitten by Russell’s viper (Vipera russelli siamensis) in Burma. Br J Haematol 69(4):513–520

124. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

125. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

126. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

127. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

128. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

129. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

130. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

131. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

132. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

133. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

134. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145

135. Kini RM (2005) The intriguing world of prothrombin activators from snake venom. Toxicon 45(8):1133–1145
Bioactive Molecules Derived from Snake Venoms with Therapeutic Potential for the Treatment…

214. Župunski V, Kordić D, Gubencćk F (2003) Adaptive evolution in the snake venom Kunitz/BPTI protein family. FEBS Lett 547(1–3):131–136

215. Verheij HM, Boffa MC, Rotchen C, Bryckaert MC, Verger R, de Haas GH (1980) Correlation of enzymatic activity and anticoagulant properties of phospholipase A2. Eur J Biochem 112(1):25–32

216. Evans HJ, Franson R, Qureshi G, Moo-Penn W (1980) Isolation of anticoagulant proteins from cobra venom (*Naja nigricollis*). Identity with phospholipases A2. J Biol Chem 255(8):3793–3797

217. Stefansson S, Kini RM, Evans HJ (1990) The basic phospholipase A2 isoenzyme from *Naja nigricollis*. Identity with phospholipases A2. J Biol Chem 265(23):14903–14911

218. Kini RM, Evans HJ (1995) The role of enzymatic inhibition in the extrinsic tenase complex by phospholipase A2 isoenzymes of *Naja nigricollis* venom. Toxiconomy 33(12):1585–1590

219. Ouyang C, Teng C-M (1972) Purification and properties of the anticoagulant principle of *Agkistrodon acutus* venom. Biochim Biophys Acta 278(1):155–162

220. Ouyang C, Yang F-Y (1975) Purification and properties of the anticoagulant principle of *Trimeresurus graninus* venom. Biochim Biophys Acta BBA 386(2):479–492

221. Atoda H, Hyuga M, Morita T (1991) The primary structure of coagulation factor IX/-factor X-binding protein isolated from the venom of *Trimeresurus flavoviridis*. Homology with asialoglycoprotein receptors, proteoglycan core protein, tetracitin, and lymphocyte Fc epsilon receptor for immunoglobulin E. J Biol Chem 266(23):14903–14911

222. Atoda H, Morita T (1993) Articles. J Biochem 113(2):159–163

223. Kini R, Stefansson S, Evans H (1988) Non-phospholipase anti-coagulant from Naja-nigricollis venom. In: Toxicon. Pergamon-Elsevier Science Ltd The Boulevard, Langford Lane, pp 28–28

224. Kini RM, Haar NC, Evans HJ (1988) Non-enzymic inhibitors of coagulation and platelet aggregation from Naja nigricollis venom are cardiotoxins. Biochem Biophys Res Commun 150(3):1012–1016

225. Kini RM, Evans HJ (1988) Mechanism of platelet effects of carboxi-derivated thrombomodulin by phospholipase A2 from *Naja nigricollis* venom. Inhibition of the extrinsic tenase complex by phospholipase A2 isoenzymes of *Naja nigricollis* venom. Toxiconomy 33(12):1585–1590

226. Mitra J, Bhattacharyya D (2014) Phosphodiesterase from *Daboia russelli* russelli venom: purification, partial characterization and inhibition of platelet aggregation. Toxicology 88:1–10

227. Trummal K, Aaspollu A, Tönismaä K, Samel M, Subbi J, Siigur J, Siigur E (2014) Phosphodiesterase from *Vipera lebetina* venom–structure and characterization. Biochimie 106:45–55

228. Kiheli H, Chëiri F, Ameziani M, Saoud S, Hariti G, Laraba-Djebri F (2021) Isolation and characterization of CD39-like phosphodiesterase (Cc-PDE) from *Cerastes cerastes* venom: molecular inhibitory mechanism of antiaggregation and anticoagulation. Protein Pept Lett 28(4):426–441

229. Chen X (2010) YU X-d, DENG M, LI H, HE Q-y, LIH J-p (2008) Purification and Characterization of 5'-nucleotidase from *Trimeresurus albolabris* Venom. Appl Biochem Biotechnol 116(12):2127–2133

230. Jasti J, Paramasivam M, Srinivasan A, Singh T (2004) Crystal structure of echisnectorin from *Echis carinatus* (Indian saw-scaled viper) at 2.4 Å resolution. J Mol Biol 343(1):167–176

231. Chen Y-L, Tsai K-W, Chang T, Hong T-M, Tsai I-H (2000) Glycoprotein IIb-binding protein from the venom of *Dendroaspis viridis* and *D. jamesonii*. Portland Press Ltd.,

232. Reese JA, Li X, Hauben M, Aster RH, Bougie DW, Curtis BR, George JN, Vesely SK (2010) Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. Blood 116(12):2127–2133

233. Shin Y, Ouyama A, Hasegawa J, Morita T (2006) Molecular cloning of glycoprotein IIb-binding protein, flavocetin-A, which inhibits platelet aggregation. Thromb Res 120(3):239–247
250. Liu C-Z, Peng H-C, Huang T-F (1995) Crotavirin, a potent platelet aggregation inhibitor purified from the venom of the snake *Crotalus viridis*. Toxiconomy 33(10):1289–1298

251. Swaim M, Chiang H-S, Huang T-F (1996) Characterisation of platelet aggregation induced by PC-3 human prostate adenocarcinoma cells and inhibited by venom peptides, trigamin and rhodostomin. Eur J Cancer 32(4):715–721

252. Knight LC, Romano JE (2005) Functional expression of bitistatin, a disintegrin with potential use in molecular imaging of thromboembolic disease. Protein Expr Purif 39(2):307–319

253. Juárez P, Comas I, González-Candelas F, Calvete JJ (2008) Evolution of snake venom disintegrins by positive Darwinian selection. Mol Biol Evol 25(11):2391–2407

254. Wang R, Kini RM, Chung MC (1999) Rhodocetin, a novel platelet aggregation inhibitor from the venom of *Calloselasma rhodostoma* (Malayan pit viper): synergistic and noncovalent interaction between its subunits. Biochemistry 38(23):7584–7593

255. Paaventhan P, Kong C, Joseph JS, Chung MC, Kolatkar PR (2005) Structure of rhodocetin reveals noncovalently bound heterodimer interface. Protein Sci 14(1):169–175

256. Dörmann D, Clemetson JM, Navdaev A, Kehrel BE, Clemetson KJ (2001) Alboaggregin A activates platelets by a mechanism involving glycoprotein VI as well as glycoprotein Ib. Blood 97(4):929–936

257. Du X-Y, Clemetson JM, Navdaev A, Magenat EM, Wells TN, Clemetson KJ (2002) Ophioluxin, a convulxin-like C-type lectin from Ophiophagus hannah (King cobra) is a powerful platelet activator via glycoprotein VI. J Biol Chem 277(38):35124–35132

258. Du X-Y, Magenat E, Wells TN, Clemetson KJ (2002) Alboluxin, a snake C-type lectin from *Trimeresurus albolabris* venom is a potent platelet agonist acting via GPIb and GPVI. Thromb Haemost 87(4):692–698

259. Du X-Y, Navdaev A, Clemetson JM, Magenat E, Wells TN, Clemetson KJ (2001) Bilinexin, a snake C-type lectin from *Agkistrodon bilineatus* bilineatus venom agglutinates platelets via GP Ibα and a2β1. Thromb Haemost 86(11):1277–1283

260. Wijeyewickrema LC, Gardiner EE, Moroi M, Berndt MC, Andrews RK (2007) Snake venom metalloproteinases, crotarhagin and alborhagin, induce ectodomain shedding of the platelet collagen receptor, glycoprotein VI. Thromb Haemost 98(12):1285–1290

261. Oliveira LS, Estrovão-Costa MI, Alvarenga VG, Vivas-Ruiz DE, Faridi TM, Tu AT, El-Asmar MF (1989) Characterization of cerastobin, a thrombin-like enzyme from the venom of *Calloselasma rhodostoma* venom. J Biol Chem 264(5):3014–3018

262. Marrakchi N, Barbouche R, Guernazi S, Karoui H, Bon C, El Ayeb M (1997) Cerastobin, a serine protease from cerastes cerastes venom, with platelet-aggregating and agglutinating properties. Eur J Biochem 247(1):121–128

263. Stocker KF (1995) The influence of snake venom enzymes on blood coagulation. Pharmacol Ther 29(3):353–405

264. Paaventhan P, Kong C, Joseph JS, Chung MC, Kolatkar PR (2005) Structure of rhodocetin reveals noncovalently bound heterodimer interface. Protein Sci 14(1):169–175

265. Dörmann D, Clemetson JM, Navdaev A, Kehrel BE, Clemetson KJ (2001) Alboaggregin A activates platelets by a mechanism involving glycoprotein VI as well as glycoprotein Ib. Blood 97(4):929–936

266. Du X-Y, Clemetson JM, Navdaev A, Magenat EM, Wells TN, Clemetson KJ (2002) Ophioluxin, a convulxin-like C-type lectin from Ophiophagus hannah (King cobra) is a powerful platelet activator via glycoprotein VI. J Biol Chem 277(38):35124–35132

267. Du X-Y, Magenat E, Wells TN, Clemetson KJ (2002) Alboluxin, a snake C-type lectin from *Trimeresurus albolabris* venom is a potent platelet agonist acting via GPIb and GPVI. Thromb Haemost 87(4):692–698

268. Paaventhan P, Kong C, Joseph JS, Chung MC, Kolatkar PR (2005) Structure of rhodocetin reveals noncovalently bound heterodimer interface. Protein Sci 14(1):169–175

269. Dörmann D, Clemetson JM, Navdaev A, Kehrel BE, Clemetson KJ (2001) Alboaggregin A activates platelets by a mechanism involving glycoprotein VI as well as glycoprotein Ib. Blood 97(4):929–936

270. Du X-Y, Navdaev A, Clemetson JM, Magenat E, Wells TN, Clemetson KJ (2001) Bilinexin, a snake C-type lectin from *Agkistrodon bilineatus* bilineatus venom agglutinates platelets via GP Ibα and α2β1. Thromb Haemost 86(11):1277–1283

271. Oliveira LS, Estrovão-Costa MI, Alvarenga VG, Vivas-Ruiz DE, Faridi TM, Tu AT, El-Asmar MF (1989) Characterization of cerastobin, a thrombin-like enzyme from the venom of *Calloselasma rhodostoma* venom. J Biol Chem 264(5):3014–3018

272. Stocker KF (1995) The influence of snake venom enzymes on blood coagulation. Pharmacol Ther 29(3):353–405

273. Marrakchi N, Barbouche R, Guernazi S, Karoui H, Bon C, El Ayeb M (1997) Cerastobin, a serine protease from cerastes cerastes venom, with platelet-aggregating and agglutinating properties. Eur J Biochem 247(1):121–128

274. Thromb Res 124(5):631–639

275. Tan NH (2010) Isolation and characterization of the thrombin-like enzyme from *Crotalus viridis*. Toxiconomy 33(10):1289–1298

276. Thromb Haemost 151(3):443–454

277. Pirkle H, Markland FS, Theodor I, Baumgartner R, Bajwa SS, Kirakossian H (1981) The primary structure of crotalase, a thrombin-like venom enzyme, exhibits closer homology to kallikrein than to other serine proteases. Biochem Biophys Res Commun 99(2):715–721

278. Pirkle H, Theodor I, Miyada D, Simmons G (1986) Thrombin-like enzyme from the venom of *Bitis gabonica*. Purification, properties, and coagulant actions. J Biol Chem 261(19):8830–8835

279. Pirkle H, Theodor I, Miyada D, Simmons G (1986) Thrombin-like enzyme from the venom of *Bitis gabonica*. Purification, properties, and coagulant actions. J Biol Chem 261(19):8830–8835

280. Pirkle H, Theodor I, Miyada D, Simmons G (1986) Thrombin-like enzyme from the venom of *Bitis gabonica*. Purification, properties, and coagulant actions. J Biol Chem 261(19):8830–8835

281. Pirkle H, Theodor I, Miyada D, Simmons G (1986) Thrombin-like enzyme from the venom of *Bitis gabonica*. Purification, properties, and coagulant actions. J Biol Chem 261(19):8830–8835

282. Pirkle H, Theodor I, Miyada D, Simmons G (1986) Thrombin-like enzyme from the venom of *Bitis gabonica*. Purification, properties, and coagulant actions. J Biol Chem 261(19):8830–8835

283. Pirkle H, Theodor I, Miyada D, Simmons G (1986) Thrombin-like enzyme from the venom of *Bitis gabonica*. Purification, properties, and coagulant actions. J Biol Chem 261(19):8830–8835
inhibits clot initiation and factor VIIa activity. J Biol Chem 280(52):42601–42611

285. Cecilio AB, Caldas S, Oliveira RAD, Santos AS, Richardson M, Naumann GB, Schneider FS, Alvarenga VG, Estevão-Costa MI, Fuly AL (2013) Molecular characterization of Lys49 and Asp49 phospholipases A2 from snake venom and their antiviral activities against Dengue virus. Toxins 5(10):1780–1798

286. Tripathy S, Dassarma B, Roy S, Chabalala H, Matsabisa MG (2020) A review on possible modes of actions of Chloroquine/Hydroxychloroquine: repurposing against SAR-COV-2 (COVID 19) pandemic. Int J Antimicrob Agents 56(2):106028

287. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC (2016) Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 531(7594):381–385

288. Borkow G, Ovadia M (1999) Selective lysis of virus-infected cells by cobra snake cytotoxins: A Sendai virus, human erythrocytes, and cytotoxin model. Biochem Biophys Res Commun 264(1):63–68

289. Muller VDM, Russo RR, Cintra ACO, Sartim MA, Alves-Paiva RDM, Figueiredo LTM, Sampaio SV, Aquino VH (2012) Crotoxin and phospholipases A2 from Crotalus durissus terrificus showed antiviral activity against dengue and yellow fever viruses. Toxicon 59(4):507–515

290. Pai VB, Nahata MC (1999) Nelfinavir mesylate: a protease inhibitor. Ann Pharmacother 33(3):325–339

291. Villarrubia VG, Costa LA, Díez RA (2004) Fosfolipasas A2 segregadas (sPLA2): ¿amigas o enemigas? Actores de la resistencia antibacteriana y antiviruses de la inmunodeficiencia humana? Med Clin 123(19):749–757

292. Freedberg DE, Conigliaro J, Wang TC, Tracey KJ, Callahan MV, Abrams JA, Sobieszczyk ME, Markowitz DD, Gupta A, O’Donnell MR (2020) Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. Gastroenterology

293. Zhang Y-J, Wang J-H, Lee W-H, Wang Q, Liu H, Zheng Y-T, Zhang Y (2003) Molecular characterization of Trimeresurus stejnegeri venom L-amino acid oxidase with potential anti-HIV activity. Biochem Biophys Res Commun 309(3):598–604

294. Rivero J, de Castro F, Stival A, Magalhães M, Carmo Filho J, Pfrimer I (2011) Mechanisms of virus resistance and antiviral activity of snake venoms. Journal of Venomous Animals and Toxins including Tropical Diseases 17(4):387–393

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.