Hemorrhagic Activity and Hemostatic Alterations Caused by *Cerastes cerastes* and *Daboia mauritanica*: Indicators of Viper Bite Severity in Morocco

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Abstract. Snakebite envenoming is a major global public health problem, causing approximately 5 million bites and 150,000 deaths each year, particularly in North Africa, where viper bites lead to significant morbidity and mortality. In Morocco, *Cerastes cerastes* and *Daboia mauritanica* are responsible for most severe viper envenomations. Their venoms are complex mixtures of bioactive proteins capable of inducing hemorrhage and profound disturbances in hemostasis. This study aimed to comparatively evaluate the hemorrhagic potential and coagulation effects of *C. cerastes* and *D. mauritanica* venoms using an experimental mouse model. Venoms were collected, processed, and quantified spectrophotometrically. Systemic toxicity was assessed via intraperitoneal LD_{50} assays, while local hemorrhagic activity was evaluated by measuring skin lesions following intradermal injection. Hemostatic alterations were analyzed two hours after administration of sublethal venom doses, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen concentration, and platelet counts. Results showed that *C. cerastes* venom exhibited higher systemic toxicity, stronger local hemorrhagic activity, and more pronounced coagulation disturbances than *D. mauritanica*. These effects correspond with proteomic data indicating a higher abundance of metalloproteinases and serine proteases in *C. cerastes* venom. Overall, the findings confirm that *C. cerastes* envenomation is generally more severe than *D. mauritanica* bites and provide experimental evidence linking venom composition to hemorrhagic and hemostatic effects. This information may aid in clinical assessment of envenomation severity and support the development of more targeted antivenoms.

Keywords: *Cerastes cerastes*, *Daboia mauritanica*, snakebite, viper envenomation, hemorrhage activity, coagulopathy disorders, minimum hemorrhagic dose (MHD), LD_{50}

1 Introduction

The World Health Organization (WHO) has recognized snakebite envenomation (SBE) as a neglected tropical disease responsible for causing significant morbidity and mortality worldwide, it is estimated that about 5 million cases are reported annually, resulting in about 150,000 deaths, according to the WHO 2017 records. In Morocco, this incidence is particularly grave due to two main culprits: the *Cerastes cerastes* (Saharan horned viper) and the highly dangerous *Daboia mauretanica* (Moorish viper) [1]. Viper venoms are indeed a complex mixture of proteins, enzymes, and toxins that disturb the process of blood coagulation, degrade tissues, and cause systemic coagulopathy [2].
Bleeding is one of the typical features of viper bite envenoming and might result in such conditions as haematomas, spontaneous bleeding, and multi-organ dysfunction [3].
The socioeconomic implications of SBE are far-reaching, especially for rural areas in which victims are usually young males working in farming activities that are heavily dependent on manual labor [4]. Without early and effectivel antivenom, snakebites may result in permanent disability, disfigurement, and trauma.
Venoms exhibit remarkable biochemical diversity, containing three-finger toxins (3FTxs), phospholipases A_2 (PLA_2s), metalloproteinases (SVMPs), serine proteinases (SVSPs), cysteine-rich secretory proteins (CRISPs), L-amino acid oxidases (LAAOs), and C-type lectin-like proteins (CTLPs) [5]. These molecules have various physiological targets, leading to haemotoxicity, myotoxicity, cytotoxicity, or neurotoxicity. Interestingly, despite the major clinical relevance of Moroccan vipers, there are very few reports where information on the venom effects has been synthesized at the proteomics, biological, and clinical levels. Understanding the effects provoked in the hemorrhages generated during the venom exposure is, in this way, fundamental for the prediction of the clinical outcome, as well as the development of more effective therapeutic approaches.
The proposed research focuses on: (1) evaluate hemorrhagic activity and determine the minimum hemorrhagic dose (MHD) of *C. cerastes* and *D. mauritanica* venoms and (2) the assessment of the impact of the two venoms on clotting factors (PT, aPTT, fibrinogen) and the number of platelets, in order to provide a comprehensive understanding of the impact of viper bites, these findings should inform the assessment of bite severity and guide therapeutic strategies.

1.1 Materials and Methods

1.1.1 Animals

Swiss male mice, weighing 18-20g, 6-8 weeks-old, were supplied by the animal facility at the Institut Pasteur du Maroc. The animals were kept in a group, in standard conditions (12 hr light cycle, 22 ± 2°C, 50-60% R.H., food, and water freely available). All animal experiments were conducted in accordance with internationally accepted standards for the use of animals in laboratories, as recommended by the World Health Organization Guide for Animal Experiments, and in agreement with the European directive 2010/63/EU.

1.1.2 Venoms

Venom samples were collected from *Cerastes cerastes* and *Daboia mauritanica* specimens maintained at the animal facility of the Institut Pasteur of Morocco. The samples were centrifuged at 3,000 rpm for 30–40 minutes at 4 °C, lyophilised and stored at −20 °C until use. These species were collected in the Drâa–Tafilalet region, particularly in the province of Errachidia (figure 1), which presents a highly diversified environment encompassing mountainous areas, rocky plateaus (Hamadas), and desert ecosystems. The morphological and climatic heterogeneity of this transitional zone supports the coexistence of both species [6] making Errachidia an ideal location for venom studies in reptiles adapted to arid and semi-arid environments

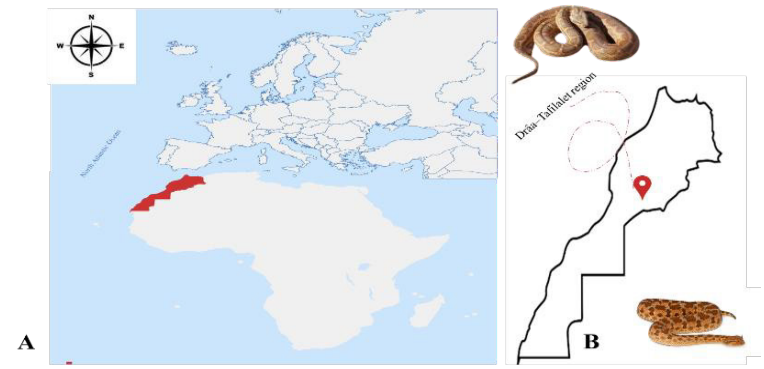

Fig. 1. (A) Geographical Location of Morocco within Africa, (B) Indicating the Collection Site (Errachidia)

1.2 Protein Quantification

The protein concentration in the supernatant was determined in triplicate by measuring absorbance at 280 nm using a VWR® Nano Spectrophotometer (200–800 nm, VWR International, Radnor, PA, USA). Quantification was based on the presence of aromatic residues (tyrosine and tryptophan) and an extinction coefficient of 1.0 (A_{280} = 1.0 for 1 mg/mL). Venoms were diluted in 0.1 M phosphate buffer (pH 7.4) [7] .

1.3 Lethal Dose (DL50)

The median lethal dose (LD_{50}) was determined according to the standard procedure described by [8] . Groups of six mice (18–20 g) received intraperitoneal injections of increasing venom doses in a constant volume of 0.5 mL. Mortality was recorded over a 24-hour observation period, and the LD_{50} values were calculated using GraphPad Prism version 7.

1.4 Determination of Minimum Hemorrhagic Dose (MHD)

The hemorrhagic activity of *Cerastes cerastes* and *Daboia mauritanica* venoms was evaluated using the mouse skin test [9] . Groups of mice received intradermal injections of increasing venom doses (50 µL in phosphate-buffered saline, PBS) into the shaved dorsal skin. Control animals received 50 µL PBS alone. Two hours after injection, mice were euthanized, and the dorsal skin was carefully excised. Hemorrhagic lesions were measured, and the MHD was defined as the smallest venom dose producing a hemorrhagic lesion of 10 mm in diameter.

1.5 Hemostatic Activity

Mice were injected with a sublethal dose of *Cerastes cerastes* venom (*Cc*, 0.25 µg/mouse, corresponding to 1/5 LD_{50}) or *Daboia mauritanica* venom (*DM*, 0.40 µg/mouse, corresponding to 1/5 LD_{50}). Blood samples were collected 2 h post-injection from the cephalic vein, a superficial vein located on the lateral side of the forelimb, along the radius, between the elbow and the wrist, of anesthetized mice using sterile syringes. Samples were immediately transferred into tubes containing 3.8% sodium citrate for coagulation assays or into EDTA tubes for platelet counts. Citrated blood samples were centrifuged at 4,000 rpm for 10 min at 4 °C to obtain platelet-poor plasma (PPP), which was stored at −80 °C until analysis.
Hemostatic parameters, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen concentration, were determined to evaluate the effects of the venoms on the coagulation profile. The platelet count was conducted on EDTA anticoagulated samples using an automated hematology analyzer

1.6 Statistical Analysis

The data for MHD and haemostatic parameters were analysed using GraphPad Prism version 7. Differences between the venom groups were assessed using a one-way ANOVA, followed by a Tukey's post hoc test for multiple comparisons. A p-value of less than 0.05 was considered statistically significant. Correlations between venom activity, coagulation parameters and published proteomic/clinical data were evaluated using the Pearson correlation coefficient.

2 Results

2.1 Lethal Dose (DL50)

The values for DL_{50} were calculated in mice to determine the systemic toxicity for *Cerastes cerastes* and *Daboia mauritanica* venom. As shown in Table 1, *C. cerastes* venom exhibited a DL_{50} of 1.25 ± 0.12 µg/mouse, which was lower than that of *D. mauritanica* (2.10 ± 0.15 µg/mouse). This indicates that *C. cerastes* venom is more systemically toxic than *D. mauritanica* venom.

The higher toxicity of *C. cerastes* venom may be attributed to a greater abundance of potent enzymatic components, such as metalloproteinases, serine proteases, and other toxins affecting hemostasis and tissue integrity [10]

These results highlight the differences in systemic toxicity between the two viper species, which may reflect variations in venom composition.

Table 1. Lethal dose (DL_{50}) values of *Cerastes cerastes* and *Daboia mauritanica* venoms in mice.

Venom	DL50 (µg/mouse) ± SD
C. cerastes	1.25 ± 0.12
D. mauritanica	2.10 ± 0.15

2.2 Determination of Minimum Hemorrhagic Dose (MHD) in Relation to DL_{50}

The minimum hemorrhagic dose (MHD) of *Cerastes cerastes* and *Daboia mauritanica* venoms was determined using the mouse skin test and expressed relative to their systemic toxicity (DL_{50}). As shown in Table 2, *C. cerastes* venom exhibited a markedly lower MHD (0.128 ± 0.01 µg/mouse), corresponding to approximately 10% of its DL_{50} (1.25 µg/mouse). In contrast, the MHD of *D. mauritanica* (0.63 ± 0.04 µg/mouse) represents about 30% of its DL_{50} (2.10 µg/mouse). These data indicate that *C. cerastes* venom has a higher hemorrhagic potency relative to its systemic toxicity, whereas *D. mauritanica* requires a larger fraction of its lethal dose to induce comparable local hemorrhage.
The corresponding lesion areas were 12.5 ± 1.2 mm² for *C. cerastes* and 11.0 ± 1.5 mm² for *D. mauritanica*, confirming that *C. cerastes* venom induces more intense local hemorrhage. This effect is likely due to a higher content of metalloproteinases, which rapidly degrade the vascular basement membrane and disrupt microvasculature.
These results highlight that *C. cerastes* venom is highly hemorrhagic even at doses far below its lethal dose, reflecting its potent enzymatic composition and providing a rationale for selecting sublethal doses for hemostatic and systemic studies

Table 2. Minimum hemorrhagic dose (MHD), fraction of DL_{50}, and corresponding lesion areas induced by *C. cerastes* and *D. mauritanica* venoms.

Venom	MHD (µg/mouse) ± SD	% of DL_{50}	Lesion area (mm²) ± SD
C. cerastes	0.128 ± 0.01	10%	12.5 ± 1.2
D. mauritanica	0.63 ± 0.04	30%	11.0 ± 1.5

2.3 Hemostatic Activity

The effects of *Cerastes cerastes* and *Daboia mauritanica* venoms on hemostatic parameters were evaluated in mice 2 h post-injection. Both venoms significantly altered coagulation and platelet indices compared to the control group (Table 3, Figure 2).
1) Prothrombin time (PT) and activated partial thromboplastin time (aPTT): *C. cerastes* venom markedly prolonged PT to 18.4 ± 1.2 s and aPTT to 42.6 ± 2.0 s, whereas *D. mauritanica* venom increased PT to 16.2 ± 1.0 s and aPTT to 35.8 ± 1.7 s, compared with control values of 12.1 ± 0.8 s and 28.5 ± 1.5 s, respectively. These findings indicate that both venoms impair the extrinsic and intrinsic coagulation pathways, with more pronounced effects observed for *C. cerastes*.
2) Fibrinogen concentration: Plasma fibrinogen levels decreased significantly from 2.9 ± 0.2 g/L in controls to 1.4 ± 0.1 g/L for *C. cerastes* and 1.9 ± 0.2 g/L for *D. mauritanica*, reflecting venom-induced consumption of clotting factors.
3) Platelet counts: Thrombocytopenia was evident, with platelet counts dropping from 950 ± 45 × 10^9/L in controls to 540 ± 38 × 10^9/L and 670 ± 40 × 10^9/L after exposure to *C. cerastes* and *D. mauritanica*, respectively.
These results demonstrate that both venoms induce significant coagulopathy and thrombocytopenia, consistent with clinical reports of coagulation disorders in Moroccan

viper envenomation [11]. The more pronounced effects observed for *C. cerastes* correlate with its higher systemic toxicity and hemorrhagic potency.

Table 3. Effects of *C. cerastes* and *D. mauritanica* venoms on hemostatic parameters in mice.

Parameter	Control ± SD	*C. cerastes* ± SD	*D. mauritanica* ± SD
PT (s)	12.1 ± 0.8	18.4 ± 1.2	16.2 ± 1.0
aPTT (s)	28.5 ± 1.5	42.6 ± 2.0	35.8 ± 1.7
Fibrinogen (g/L)	2.9 ± 0.2	1.4 ± 0.1	1.9 ± 0.2
Platelets (×10⁹/L)	950 ± 45	540 ± 38	670 ± 40

2.4 Comparative Summary of Venom Activities and Hemostatic Effects

A comparative evaluation of *Cerastes cerastes (Cc)* and *Daboia mauritanica (Dm)* venoms reveals distinct differences in systemic toxicity, haemorrhagic potential and haemostatic alterations (see Table 4).

Systemic toxicity (DL_{50}): *C. cerastes* venom exhibited a DL_{50} of 1.25 µg/mouse, which is nearly twofold lower than that of *D.mauritanica* (2.10 µg/mouse). This indicates substantially higher systemic lethality.

- Local haemorrhagic activity (MHD): The minimum haemorrhagic dose of *C. cerastes* (0.128 µg/mouse) was approximately five times lower than that of *D. mauritanica* (0.63 µg/mouse), confirming its stronger capacity to induce local haemorrhage.

- Hemostatic parameters: Both venoms significantly altered coagulation indices compared to controls, but the effects were consistently more pronounced with *C. cerastes.* Prothrombin time (PT) and activated partial thromboplastin time (aPTT) increased to 18.4 seconds and 42.6 seconds, respectively, compared to 16.2 seconds and 35.8 seconds for *D. mauritanica*. Plasma fibrinogen levels decreased to 1.4 g/L with *C. cerastes* and to 1.9 g/L with *D. mauritanica*, while platelet counts dropped to 540 ×10⁹/L and 670 ×10⁹/L, respectively. These results suggest that *C. cerastes* envenomation leads to greater consumption of coagulation factors and more severe thrombocytopenia.
- Proteomic and biochemical correlates: The high metalloproteinase (MMP-III) and serine protease content of *C. cerastes* venom is associated with its intense haemorrhagic and coagulopathic effects. By contrast, *D. mauritanica* venom exhibits moderate metalloprotease activity, but has a higher lectin content which may modulate platelet aggregation and limit local haemorrhaging to some extent.

Overall, *C. cerastes* venom is more toxic and proteolytically active, producing rapid systemic and local haemostatic disturbances. While still pathogenic, *D. mauritanica* venom shows less aggressive haemorrhagic and coagulopathic activity, which is consistent with the moderate clinical manifestations reported in Moroccan cases.

Table 4: Comparative hemorrhagic, coagulopathic, and proteomic profiles of Moroccan *Dm* and *Cc* vipers.

Activity / Parameter	*C. cerastes (Cc)*	*D. mauritanica (DM)*	Clinical Relevance
DL_{50} (µg/mouse)	1.25	2.10	Higher systemic toxicity for *Cc*
MHD (µg/mouse)	0.128	0.63	Stronger local hemorrhage in *Cc*
PT (s)	18.4	16.2	Greater coagulopathy with *Cc*
aPTT (s)	42.6	35.8	Confirms prolonged clotting for *Cc*
Fibrinogen (g/L)	1.4	1.9	Higher consumption in *Cc* bites
Platelets ($\times 10^9$/L)	540	670	Thrombocytopenia more severe with *Cc*
Metalloproteinase content	High (P-III)	Moderate	Explains MHD and coagulopathy differences
Serine protease activity	High	Moderate	Contributes to coagulation alterations
Disintegrins / Lectins	Moderate	High (lectins)	Platelet modulation, less local hemorrhage
Clinical severity	Severe	Moderate	Consistent with experimental and clinical data [12–14]

3 Discussion

In Morocco, viper envenomation account for more than 70% of severe snakebite cases, representing a major public health concern due to their rapid progression and life-threatening complications. Among Moroccan vipers, *Cerastes cerastes (Cc) and Daboia mauritanica (Dm)* are the most clinically relevant species, making the characterization of their venom activities essential for improving clinical management, antivenom development, and predicting envenomation severity.

Our results demonstrate that *Cc* venom exhibits markedly higher hemorrhagic and systemic toxicity than *Dm* venom, as evidenced by its lower DL_{50} (1.25 µg/mouse versus 2.10 µg/mouse) and lower MHD (0.128 µg/mouse versus 0.63 µg/mouse). These findings indicate that *Cc* venom is more potent, requiring smaller doses to induce systemic lethality and local hemorrhage. Importantly, the MHD of *Cc* represents only a small fraction of its LD_{50}, indicating that severe local hemorrhage can occur at sublethal doses, highlighting hemorrhage as a key determinant of envenomation severity. The corresponding lesion areas further confirm that *Cc* venom produces more intense local hemorrhage than *Dm* (12.5 ± 1.2 mm² versus 11.0 ± 1.5 mm²). Clinically, these results align with observations in Morocco, where *Cc* bites are frequently associated with severe local bleeding, rapid swelling, tissue necrosis, and coagulopathy, whereas *Dm* envenomations typically produce moderate and slower-onset systemic manifestations [12–14].

Proteomic analysis provides a mechanistic explanation for these differences. *Cc* venom is enriched in P-III snake venom metalloproteinases (SVMPs), serine proteases, and disintegrins, which synergistically degrade vascular basement membranes, consume coagulation factors, and induce thrombocytopenia. P-III SVMPs are known to target basement membrane components such as collagen IV and laminin, leading to capillary disruption and blood extravasation. These combined actions lead to extensive local tissue damage and systemic coagulopathy. In contrast, *Dm* venom contains a mixture of

metalloproteinases and C-type lectins, which primarily modulate platelet aggregation, resulting in moderate hemorrhagic activity despite noticeable systemic effects [15].

Consistent with this proteomic profile, both venoms significantly altered hemostatic parameters in mice. *Cc* venom markedly prolonged prothrombin time (PT: 18.4 ± 1.2 s) and activated partial thromboplastin time (aPTT: 42.6 ± 2.0 s) compared to *Dm* venom (PT: 16.2 ± 1.0 s; aPTT: 35.8 ± 1.7 s) and control values (PT: 12.1 ± 0.8 s; aPTT: 28.5 ± 1.5 s). Plasma fibrinogen levels decreased more sharply with Cc (1.4 ± 0.1 g/L) than *Dm* (1.9 ± 0.2 g/L), reflecting a more severe consumption coagulopathy, while platelet counts were reduced to 540 ± 38 $\times 10^9$/L and 670 ± 40 $\times 10^9$/L, respectively. These results demonstrate that *Cc* envenomation produces more pronounced consumption of coagulation factors and severe thrombocytopenia, confirming its higher clinical severity. The severity of *Cc* envenomation is largely attributed to its potent P-III SVMPs, whose synergistic action with serine proteases accelerates fibrinogen depletion and coagulation factor consumption, whereas the less pronounced effects of *Dm* result from its lower metalloproteinase activity and higher proportion of lectin-like toxins that mainly interfere with platelet function [16]

The correlation between proteomic composition and biological activity highlights that local hemorrhage is driven primarily by SVMP concentration, systemic coagulopathy depends on both SVMP and serine protease activities, and thrombocytopenia is enhanced by disintegrins and platelet-modulating toxins. Together, these mechanisms define *Cc* venom as a “triple threat,” combining local vascular destruction, systemic coagulopathy, and platelet dysfunction, consistent with its higher clinical severity. The concordance between experimental and clinical data suggests that parameters such as DL_{50}, MHD, and coagulation indices may serve as predictive markers of envenomation severity in viperid bites.

Clinically, *Cc* envenomation requires urgent administration of specific antivenom and close monitoring of coagulation parameters, given the occurrence of severe hemorrhagic and coagulopathic effects at sublethal venom doses, whereas *Dm* bites, although still serious, generally progress more slowly. From a therapeutic perspective, targeted antivenom formulations should prioritize the neutralization of P-III metalloproteinases and serine proteases to effectively mitigate hemorrhagic and systemic coagulopathic effects. Moreover, characterization of these venoms provides valuable insights into hemostatic disturbances and highlights their potential as sources of novel pharmacological tools. Venom-derived proteins that modulate coagulation and platelet function represent promising templates for the development of new drugs targeting thrombotic and hemostatic disorders [17].

In conclusion, a comprehensive understanding of African viper venom composition not only improves the clinical management of snakebite envenoming but also supports the exploration of biomedical applications. By integrating toxicological, proteomic, and hemostatic data, the present study provides crucial information for predicting envenomation severity, guiding clinical interventions, and designing more effective and targeted antivenoms, particularly in regions where viper bites constitute the majority of severe cases.

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