REVIEW OPEN ACCESS

Journal of
Venomous Animals and Toxins
including Tropical Diseases

ISSN 1678-9199

www.jvat.org

Pulmonary involvement from animal toxins: the cellular mechanisms

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Abstract

Venomous animals and their venom have always been of human interest because, despite species differences, coevolution has made them capable of targeting key physiological components of our bodies. Respiratory failure from lung injury is one of the serious consequences of envenomation, and the underlying mechanisms are rarely discussed. This review aims to demonstrate how toxins affect the pulmonary system through various biological pathways. Herein, we propose the common underlying cellular mechanisms of toxin-induced lung injury: interference with normal cell function and integrity, disruption of normal vascular function, and provocation of excessive inflammation.

Viperid snakebites are the leading cause of envenomation-induced lung injury, followed by other terrestrial venomous animals such as scorpions, spiders, and centipedes. Marine species, particularly jellyfish, can also inflict such injury. Common pulmonary manifestations include pulmonary edema, pulmonary hemorrhage, and exudative infiltration. Severe envenomation can result in acute respiratory distress syndrome. Pulmonary involvement suggests severe envenomation, thus recognizing these mechanisms and manifestations can aid physicians in providing appropriate treatment.

Keywords:
lung injury
animal, toxin
cellular mechanism
pulmonary edema
pulmonary hemorrhage

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https://doi.org/10.1590/1678-9199-JVATITD-2023-0026

Received: 21 April 2023; Accepted: 11 August 2023; Published online: 18 September 2023

Backgrounds

Humans have long been fascinated by venomous animals and their venom. Animals from both terrestrial and aquatic habitats, such as wasps, bees, spiders, scorpions, and snakes, as well as fish, sea urchins, cone snails, cnidarians, and annelids, all create venom for various purposes such as predation, defense, and competition reduction [1]. Venom are abundant natural sources of biogenic amines, proteins, and peptides [2, 3]. Due to the high metabolic expense of venom generation, a wide range of potent and selective toxins have been developed [4] to specifically target key physiological components of the target species [1]. Even though venomous animals normally do not hunt humans, coevolution has equipped venom with the ability to attack human physiological structures, usually, those engaged in crucial regulatory processes or bioactivities such as cell membranes, ion channels, and receptors [5]. Despite being much smaller in size, even a small amount of their poisons can result in catastrophic injury or even death.

One of the serious consequences of animal toxins is respiratory failure from neuromuscular dysfunction or lung injury, whose underlying mechanisms are rarely discussed. This review demonstrates how specific toxin components can cause lung injury through various biological pathways.

Mechanisms for pulmonary involvement by animal toxins

1As early as the Anthozoa phylogeny (sea anemones and corals), some animals harness the capability of producing toxins [6]. Over generations, significant proportions of the common (ancestral) or lineage-specific genes and gene families [5, 6] responsible for toxin production affect the fundamental physiology of the target organisms, including humans.

Because toxins are readily distributed into the systemic circulation and various organs through the vascular and lymphatic systems once released and injected, one of the serious consequences of animal toxins is respiratory failure resulting from lung injury [7]. With the high blood flow and extensive vascular bed, the pulmonary system serves as a major target for toxins. In addition to altering the physiology and architecture of gas exchange barriers, the diverse mixture of toxins also dysregulated the host immune response [8].

Envenomation can cause lung injury through three broad categories of toxin-induced end-organ damage: pulmonary, non-pulmonary, and local site of toxin entry (Figure 1). Many toxins exert systemic effects that indirectly raise pulmonary hydrostatic pressure and result in pulmonary edema. Several case reports and reviews have highlighted cardiotoxicity leading to

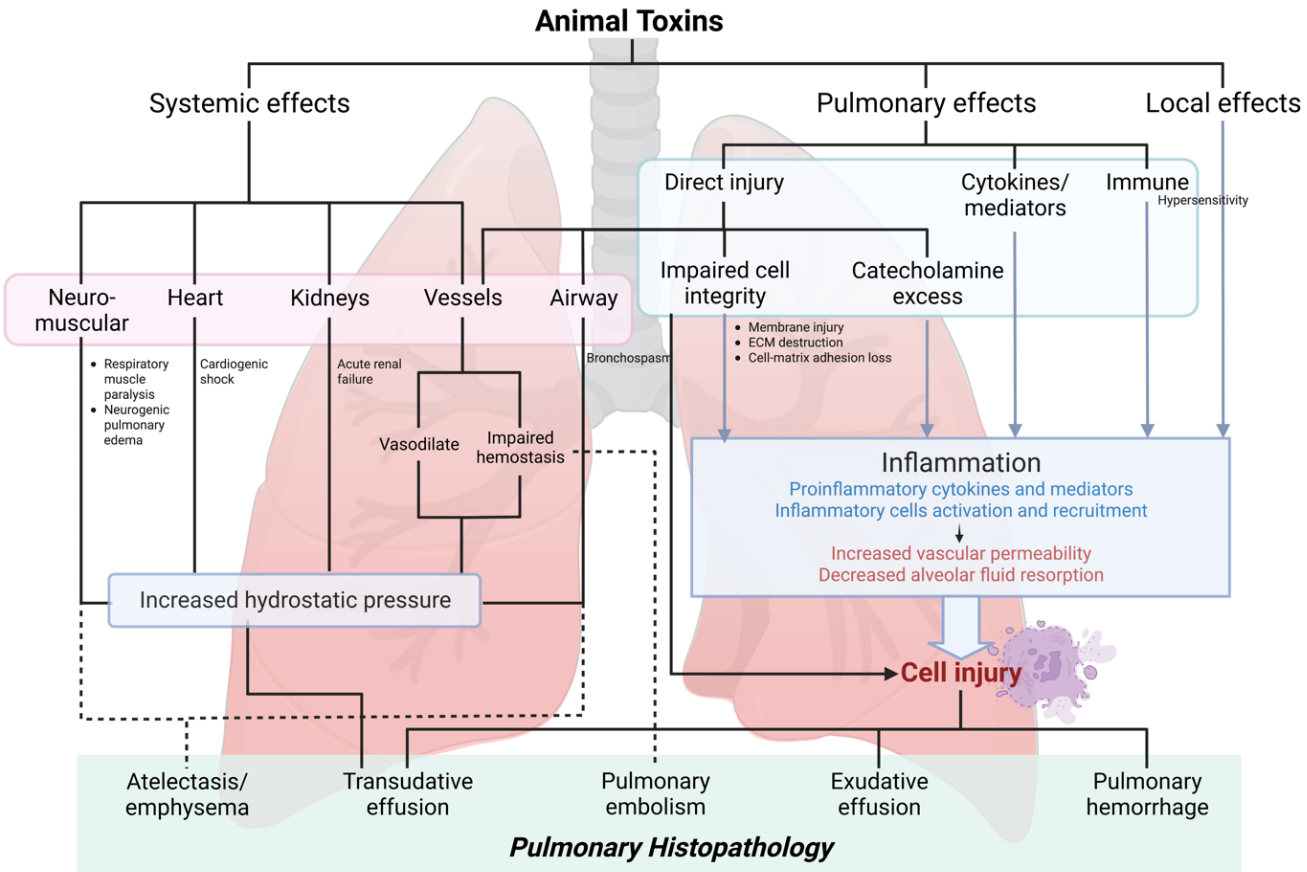

Figure 1. Pathophysiology of animal toxin-induced lung injury and the resulting pulmonary histopathology. Three main toxin-induced lung injuries include damages to the pulmonary system, non-pulmonary systems, and damages at the site of toxin entry. Toxins can exert systemic effects, leading to elevated pulmonary hydrostatic pressure and subsequent development of pulmonary edema. Additionally, toxins can directly harm the lungs or contribute to secondary damage through local or systemic inflammation. The observed histopathology is influenced by the underlying pathophysiological mechanism. ECM: extracellular matrix.

cardiodepression, myocarditis, and myocardial infarction [9–13]; nephrotoxicity leading to volume overload [14, 15]; neurotoxicity leading to respiratory muscle paralysis and ventilatory failure [16, 17], and neurogenic pulmonary edema [18]. These causes of pulmonary injuries are mentioned elsewhere. Several toxins directly damage the lungs by increasing airway resistance, which leads to atelectasis or emphysema [19]. On a microscopic level, many toxins cause pulmonary edema (transudate or exudates), hemorrhage, or embolism through numerous cellular mechanisms, most of which are followed by lung inflammation whose pathophysiologic derangements resemble those of acute lung injury or acute respiratory distress syndrome (ARDS) [20, 21].

The alveolar unit, a critical part of the pulmonary system, is lined by a single-layer endothelium of alveolar type II (ATII) and flat alveolar type I (ATI) cells to form a selective barrier to fluids and solutes. To maximize gas exchange, these cells remove excess airspace fluid by creating an osmotic gradient through the absorption of sodium by apical epithelial sodium channels (ENaC) and basolateral Na^+/K^+ ATPase pumps, and water by aquaporin channels (AQP) such as AQP5. The electrochemical and osmotic gradients are also maintained by a chloride channel called cystic fibrosis transmembrane conductance regulator (CFTR) [21, 22]. The alveolar unit also consists of essential structural extracellular matrix (ECM) components such as basement membrane (BM) and interstitial connective tissues [23], and immune cells such as alveolar macrophages, neutrophils, and monocytes [20] (Figure 2). Understanding the structural basis of the pulmonary system provides insight into lung pathologies induced by toxins [21]. In this article, we propose the common underlying cellular mechanisms by which animal toxins can cause lung injury (Figure 3).

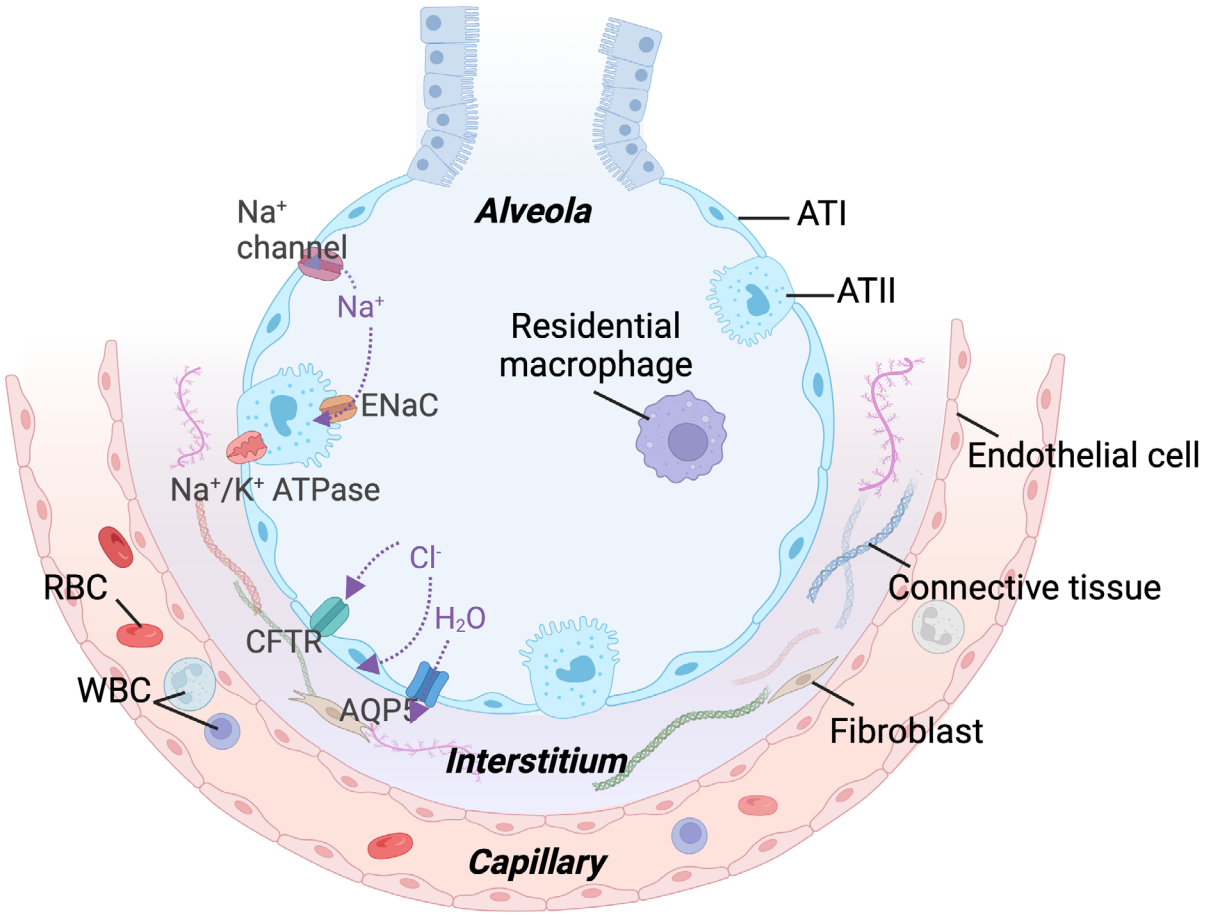

Figure 2. Normal cellular structures and important ion channels of the alveolus. The alveolar unit consists of a single-layer endothelium composed of ATI and ATII cells, creating a selective barrier for fluids and solutes. The alveolar fluid is primarily regulated through the absorption of sodium via ENaC and basolateral Na^+/K^+ ATPase pumps, as well as water through AQP5 channels, while the electrochemical and osmotic gradients are maintained by the CFTR chloride channel. Additionally, the alveolar unit includes structural extracellular matrix components and immune cells such as alveolar macrophages, neutrophils, and monocyte. AT: alveolar type; AQP5: aquaporin 5; CFTR: cystic #brosis transmembrane conductance regulator; ENaC: epithelial sodium channel; Na^+/K^+ ATPase: sodium/potassium ATPase pump; RBC: red blood cell; WBC: white blood cell; Na^+: sodium, K^+: potassium, Cl^-: chloride, H_2O: water.

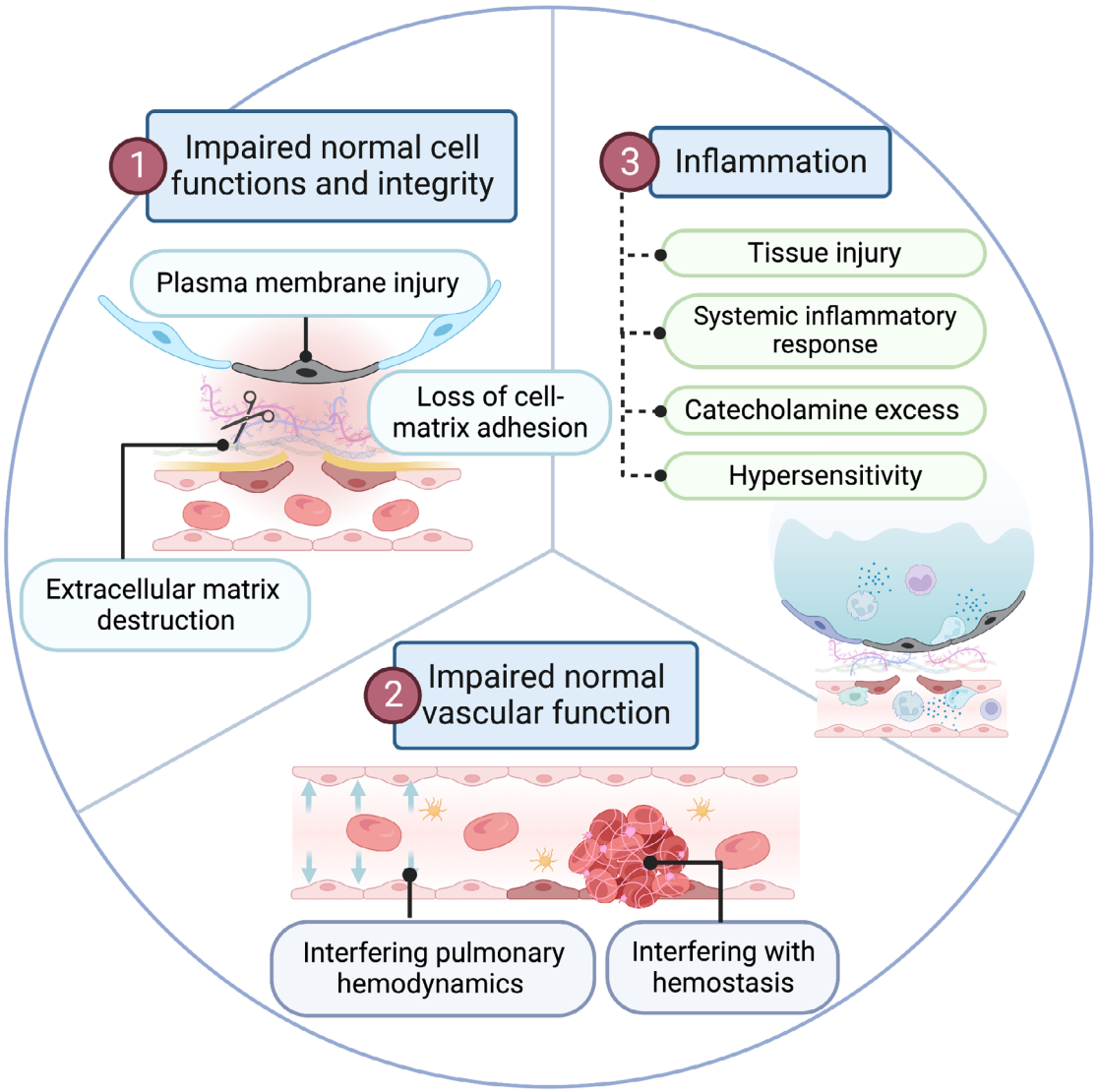

Figure 3. Proposed cellular mechanisms of animal toxin-induced lung injury. The figure illustrates the common mechanisms that collectively contribute to the development of lung injury from animal toxin exposure. The mechanisms include interference with essential cellular functions and integrity necessary for cell survival, disruption of normal vascular function through diverse mechanisms of action, and induction of excessive inflammation, which can indirectly contribute to cellular damage.

Impaired normal cell functions and integrity

Plasma membrane injury

Cell membrane integrity is crucial for maintaining cellular compartments and ionic homeostasis. Disruptions in this balance can induce secondary inflammation and cell death [24, 25]. Membrane damage can be caused by enzyme digestion or the insertion of positively charged amphipathic peptides (pore formation) [26] found in many venomous species, including cnidarians, fish, insects, arachnids, and snakes [27]. The common membrane toxins include:

a) Phospholipase A_2 (PLA_2):

PLA_2 is widely distributed among venomous animals [28]. This fundamental and prevalent enzyme toxin mimics the mammalian housekeeping PLA_2, hydrolyzing the glycerophospholipids in cytosolic organelles and plasma membranes, leading to non-specific membrane disruption, loss of cytosolic calcium homeostasis, and eventual cell degeneration. Because of its non-specific membrane affinity, PLA_2 produces various effects including neurotoxicity, myotoxicity, cardiotoxicity, and local tissue damage [29].

Snake venom PLA2

The basic PLA_2 from Russell's viper (*Daboia russelli*) (VRV-PL-VIIIa) can induce pulmonary hemorrhage when injected intraperitoneally or intravenously in mice [30]. *In vivo* studies administering PLA_2 from the Javan spitting cobra (*Naja sputatrix*) intravenously and intratracheally in rats resulted in marked

pulmonary inflammation and edema, supported by an increase in inflammatory markers and decreased protein expression of Na^+/K^+ ATPase and AQP [31]. Crotamine and crotoxin's high PLA_2 activity also suggested evident pulmonary inflammation, edema, hemorrhage, and atelectasis in mice injected with the whole venom of the South American rattlesnake (*Crotalus durissus*) intraperitoneally and intramuscularly [19, 32].

A human case report from Sri Lanka documented a lethal *Daboia russelli* bite that caused anaphylactic shock and significant renal failure, followed by pulmonary hemorrhage on day three [33]. The author hypothesized that the lung injury was rather caused by PLA_2 in the venom than by a minor degree of hemolysis and coagulopathy. In India, one patient survived severe envenomation from a *Daboia russelli* but developed consumptive coagulopathy, acute renal failure, rhabdomyolysis, paralysis, and diffuse alveolar hemorrhage persisting a week after the bite. Plasmapheresis was proposed to aid the patient's recovery [34].

b) Cytotoxins:

Most venoms amplify tissue damage synergistically along with PLA_2 with cytotoxins. The toxins are highly basic, positively charged, amphipathic proteins that can create pores on the negatively charged cell membranes [35, 36]. Some types of cytotoxins, called cell-penetrating peptides (CPP), a family of short (less than 35 amino acids) naturally occurring or artificially produced peptides can also break cell membranes [37]. Some CPPs include melittin, anoplin, and mastoparans from wasps, latarcin from spiders, crotamine, crotalicidin, and elapid cathelicidin-related antimicrobial peptides from snakes, and pardaxin from fish skin [27].

Cytotoxins in terrestrial venomous animals (snakes, spiders, insects) and marine animals

Most cytotoxins belong to the three-finger toxin superfamily and are mostly found in cobra snake venom [35]. Other sources include sea anemones, cnidarians like multi-tentacled box jellyfish (*Chironex fleckeri*), and Portuguese man o' war (*Physalia physalis*) [6, 38]. Spider cytotoxin, such as phospholipase D (sphingomyelinase D) from recluse spiders (*Loxosceles* spp.), can directly disrupt the alveolar cell membrane and indirectly lead to cytokine storms resulting in pulmonary edema [39, 40]. The presence of proteases, cytotoxins, and vasodilative peptides in stonefish venom (family Synanceja) caused lung edema, inflammation, and hemorrhage in animals and cardiogenic or non-cardiogenic pulmonary edema in human case reports [41, 42]. Jellyfish venom (genus *Nemopilema*) contains cytotoxins and metalloproteinases with pore-forming properties, which were suspected to cause cardiogenic shock and increase vascular permeability leading to fatal cases with pulmonary edema [43, 44]. Cantharidin found in blister beetles (genus *Epicauta*) has an acantholytic property and has been shown to cause cardiac injury, pulmonary edema, and subpleural hemorrhage in alpacas [45].

Extracellular matrix (ECM) destruction

The ECM area contains various connective tissues, including collagen, elastin, and proteoglycans [46], which provide mechanical and functional stability to capillaries and alveoli, making it a common target of exogenous toxins.

a) Matrix metalloproteinases (MMPs):

The proteinase enzymes weaken capillary walls, collapse basement membranes, and promote the spread of toxins by hydrolyzing many structural proteins of the basal lamina component and surrounding ECM known as matrix metalloproteins [47]. These injuries increase the risk of pulmonary hemorrhage and contribute to inflammation by releasing numerous mediators present in alveolar exudates [47, 48]. Venom of jellyfish, cone snails, centipedes, scorpions, and snakes all contain large amounts of MMPs [6], such as snake venom MP (SVMP), which is often referred to as hemorrhagins due to its ability to cause bleeding.

MMPs in snake venom

SVMPs are ubiquitous in viperid venom [49]. Numerous animal studies have provided supporting evidence that SVMPs, such as Jararhagin, the main SVMP found in the venom of *Bothrops asper* and *Bothrops jararaca*, primarily target the basal lamina of alveolar cells, leading to pulmonary hemorrhage [50–52]. The destructive effects on cellular structures can be further intensified by PLA_2 [53, 54], another abundant enzyme in venom, as demonstrated by the increased detachment of endothelial cells when both enzymes are present [55]. Additionally, a C-type lectin (CTL) called aspercetin, which is another venom component, has been identified to potentiate the hemorrhagic effect [51].

MP activities in the venom of hump-nosed pit vipers (*Hypnale* spp.) have also been implicated in inducing pulmonary edema and hemorrhage *in vivo* [56]. The venom of the Gaboon pit viper (*Bitis gabonica*) has been shown to cause pulmonary edema in animal studies, possibly due to the venom's effect on the cardiovascular system or the hemorrhagic component damaging pulmonary endothelial cells [57, 58].

SVMP activities in venom have been implicated in pulmonary hemorrhage in several human case reports. A bite from *Bothrops jararacussu*, a pit viper with a high proportion of hemorrhaging, killed a 36-year-old woman within 45 minutes. Her autopsy revealed pulmonary hemorrhage and disseminated microthrombi in alveolar vessels [59]. Sri Lankan *Daboia russelli* venom, containing MP and other hemorrhagic toxins, was suspected of causing massive pulmonary hemorrhage in a 30-year-old man six hours after the bite, along with paralysis, renal failure, rhabdomyolysis, and deep vein thrombosis [60]. Pulmonary hemorrhage was also reported in patients bitten by *Hypnale hypnale*, accompanied by symptoms of thrombotic microangiopathy (TMA) such as renal failure, coagulopathy, and dry gangrene of both feet [61]. One fatal case from *H. hypnale* resulted in severe systemic bleeding, including intracerebral,

endocardial, pericardial, and pulmonary hemorrhage and TMA. Despite aggressive resuscitation with blood products and hemodialysis, blood loss continued until death due to unavailable antivenom [62]. Autopsies of sudden death cases after *H. hypnale* bites have also revealed myocardial and pulmonary hemorrhage [63].

b) Hyaluronidase:

Nearly all vertebrate cells contain hyaluronic acid, a negatively charged glycosaminoglycan that serves as an intercellular adhesive. Hyaluronidase damages local tissue by hydrolyzing lung interstitial hyaluronan, which inadvertently facilitates poison dispersal [64]. Hyaluronidases can be found in the secretions of nematodes and leeches, as well as in the venom of snakes, scorpions, centipedes, spiders, insects, fish, and lizards [64–66]. In contrast to MMPs, animal studies or human case reports of lung injuries by hyaluronidase were not evident.

Loss of cell-matrix adhesion

Integrins mediate the adherence of eukaryotic cells to the ECM. On the alveolar surface, they function as extracellular receptors that regulate cell adhesion, proliferation, and migration to maintain alveolar homeostasis. Disintegrins and CTL derived from snake venom impair these integrin functions [24]. Animal-toxin disintegrins preferentially interact with certain types of alveolar integrins, particularly those that anchor to ECM collagens [67], and endothelial integrins, specifically vascular cell adhesion molecule-1 (VCAM-1) [24]. Disintegrins are generally not harmful (25), but dysfunctional integrins of alveolar epithelial cells might indirectly cause lung injury by triggering an inflammatory response [68].

Impaired normal vascular function

Toxins interfering with hemostasis

Pulmonary hemorrhage from snake venom

Toxins, particularly those from snakes, can disrupt systemic hemostasis and lead to pulmonary hemorrhage [33, 50, 51, 59] and pulmonary embolism [69]. These toxins are capable of causing direct anti/prothrombotic effects, platelet dysfunction, indirect consumptive coagulopathy from secondary endothelial injuries, such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome [16], or enhancing other toxins hemorrhagic effects [51]. The detailed mechanisms of coagulopathy are reviewed elsewhere [70, 71]. The typical peptides/proteins involved in these events are as follows:

a) Proteases:

Serine protease – These enzyme toxins affect different stages of blood coagulation and are frequently found in viperid snakes, spiders, and scorpions [72]. They can act either as pro-coagulants through fibrin synthesis, factor V activation, or platelet aggregation, or as anti-coagulants through fibrinolysis, plasminogen activation, or protein C activation [73].

MMP – Animal MMP has fibrinolytic properties and can proteolyze clotting proteins, which, in addition to injuring the BM, can cause pulmonary hemorrhage such as jararhagin found in *Bothrops jararaca* [71]. Similar to serine protease, several MMPs can promote thrombosis by activating prothrombin such as ecarin found in saw-scaled pit viper (*Echis carinatus*), and factor X such as RVV-X, a factor X activator, found in *Daboia russelli* [71].

b) Disintegrin and C-type lectin (CTL) toxins:

Disintegrins, which can bind to platelet glycoprotein (GP) IIb/IIIa integrins, are cysteine-rich, Arg–Gly–Asp (RGD) – containing polypeptides identified in snake venom. Integrins are essential for the development of the platelet-platelet bridge and promote platelet aggregation. Because disintegrin is frequently present in complexes with metalloproteinase in SVMP classes P-II and P-III [74], it is understandable why snakebite victims have an increased risk of lung hemorrhage [73]. PIII-SVMP has a greater hemorrhagic potential due to the presence of a disintegrin-like domain that interferes with coagulation and a metalloproteinase domain that has a greater ability to hydrolyze type IV collagen and other non-fibrillar collagens in the BM-ECM network [48]. Like disintegrins, CTLs are also found in SVMP class P-III [74] and target platelet membrane integrins whose ligands include factor IX, factor X, or GPIb-mediated platelet activators [75].

c) PLA_2:

PLA_2 especially those from viperids affects several blood coagulation processes by inhibiting the prothrombinase complex and interacting with numerous coagulation-related proteins and membranes [76].

d) L-amino acid oxidases (LAAOs):

LAAOs are flavoenzymes that are present in a wide range of species, including bacteria, fungi, algae, fish, snails, and snakes (except for the Hydrophidae family) [77, 78]. They convert L-amino acid substrates into keto acids, ammonia, and hydrogen peroxide through oxidative deamination (H_2O_2). The production of H_2O_2 causes cytotoxicity to various cell types, including alveolar cells [77]. Additionally, LAAOs display both procoagulant activity by causing platelet aggregation and anticoagulant activity by weakening clots [79]. Intravenous injection of LAAO component in the pit viper *Agkistrodon blomhoffii ussurensis* venom to mice induced loss of pulmonary structure, pulmonary edema, and hemorrhage [77].

Pulmonary embolism from snake venom

While snake bites are commonly associated with hemorrhagic effects, there have also been reports of pulmonary embolisms in humans. A serine protease in *Bothrops jararacussu*

(Jararacussin-1) has potentially contributed to the lethal bite from this snake by consumption of clotting factors through promoting weak fibrinogen clots [59]. *Bothrops lanceolatus*, a snake found only in Martinique, has been linked to thrombotic phenomena. A case series of 50 *B. lanceolatus* bites documented two incidences of pulmonary embolisms [80]. Another case report documented a fatal bite from *B. lanceolatus* that resulted in brain and myocardial infarction. A necropsy revealed a rupture of the papillary muscle of the mitral valve from a growing thrombus and the presence of numerous blood clots in the brain, lungs, mesentery, kidneys, and small arterial walls. Additionally, intense angiogenesis was noted in the organizing cerebral infarcts. The formation of these blood clots and abnormal angiogenesis could be induced by the presence of MMP and vascular endothelial growth factor (VEGF), respectively, in *B. lanceolatus* venom [81]. In another case involving *B. lanceolatus*, a woman on contraceptive pills suffered from serious pulmonary embolism and disseminated intravascular coagulation (DIC) [69].

Pulmonary embolisms can occur a few days after the snake bite and are often accompanied by DIC or hypofibrinogenemia. Excessive inflammation or direct toxin effects have been hypothesized as the underlying causes [82]. A delayed massive pulmonary embolism was observed in a case involving a Mojave rattlesnake (*Crotalus scutulatus*) bite, occurring on day three despite receiving multiple doses of antivenoms [83]. Cases of viper bites in Morocco (most likely from *Vipera lebetina* or *Cerastes cerastes*) [84], Greece (*Vipera ammodytes, V. aspis, V. lebetina,* or *V. xanthina)* [85], and French western coast (*Vipera aspis* or *V. berus*) [82] also exhibited delayed acute pulmonary embolism about one week after the bite.

Toxins interfering pulmonary hemodynamics and vascular permeability

Certain peptide toxins associated with inflammation can induce vasodilation, which increases vascular permeability and blood flow to the lungs [86]. Examples of such peptides include prostaglandins, histamines [87], and components of kallikrein-kinin pathways, such as bradykinins, kininogens, and kallikrein-like enzymes that increase bradykinin synthesis, as well as angiotensin-converting enzyme inhibitors that decrease bradykinin oxidation [86]. Most of these peptides can be found in the venom of insects, frogs, and reptiles [28, 87]. The toxins found in scorpion venoms have been frequently associated with pulmonary edema in human case reports [87]. Notably, a toxin discovered in the venom of the Indian red scorpion (*Mesobuthus tamulus*) was named pulmonary edema-inducing toxin (PoTx) due to its capacity to cause lung injury *in vivo* [88].

The inflammation

Critical host response against envenomation entails innate and adaptive immune strategies aimed at venom detection, neutralization, detoxification, and symptom relief [2]. Venoms frequently offset the host's immune defense and produce even more severe symptoms. The principal causes of inflammation after envenomation include the following mechanisms.

Tissue injury

Activated toxin-injured vascular endothelium, whether local or distant from the site of injury, upregulates the expression of various mediators, including angiopoietin-2, and adhesion molecules such as intercellular adhesion molecule (ICAM), VCAM, and selectin. These mediators then attract and activate immune cells like neutrophils, macrophages, and lymphocytes [20]. Numerous proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-8, IL-6, and IL-1β, are generated, drawing in additional immune cells [21]. Cell death follows membrane lipid peroxidation by H_2O_2, nitric oxide, and oxygen species produced by neutrophils [89]. Inflammation not only damages the endothelium layer but also weakens the tight junctions (vascular endothelial (VE)-cadherin) [20] and subtly disturbs the alveolar epithelium, which is more resilient to damage. This can result in even more excessive exudative fluid leaking into the alveolar septa or alveolar space [20]. The synthesis of mediators of inflammatory cells to the site of tissue damage, in turn, starts a vicious circle of inflammation [90]. Inflammation also favors local and systemic procoagulant states by activating platelets, and inhibiting tissue plasminogen, which may account for the presence of microthrombi in acute lung injury models [91].

Inflammation dysregulates fluid homeostasis in the alveoli by the release of vasodilators such as prostaglandins, histamines, and nitric oxide from the wounded tissue [89]. Additionally, inflammatory mediators such as IL-1β, IL-8, and TNF-α inhibit channels responsible for alveolar fluid clearance including Na^+/K^+ ATPase, ENaC, CFTR, and AQP5 [21]. The mediators also increase expressions of Na^+-K^+-Cl^- cotransporter (NKCC) and CFTR (10, 90). Specifically, NKCC located on the basolateral side of alveolar cells facilitates inward transport of one molecule each of Na^+ and K^+ ions and two molecules of Cl^-. The chloride molecules are then transported apically through CFTR (10) promoting chloride-driven alveolar fluid secretion (Figure 4).

Systemic inflammatory response syndrome

In addition to directly injuring tissues, toxins produced by venomous animals can induce excessive inflammation by triggering a massive cytokine release. This phenomenon, known as a cytokine storm, can lead to a life-threatening condition called systemic inflammatory response syndrome (SIRS) [92] or cytokine release syndrome [93]. Symptoms and signs typically include fever [94], tachycardia, and tachypnea, as well as changes in immune cells populations such as leucocytes, and elevated levels of circulating acute phase reactants and cytokines, such as IL-1, IL-6, IFN-γ, and TNF-α [95]. If the inflammatory response outweighs the anti-inflammatory one and persists over time, multi-organ dysfunction may develop [96], including the aforementioned lung injury. Following envenomation, the

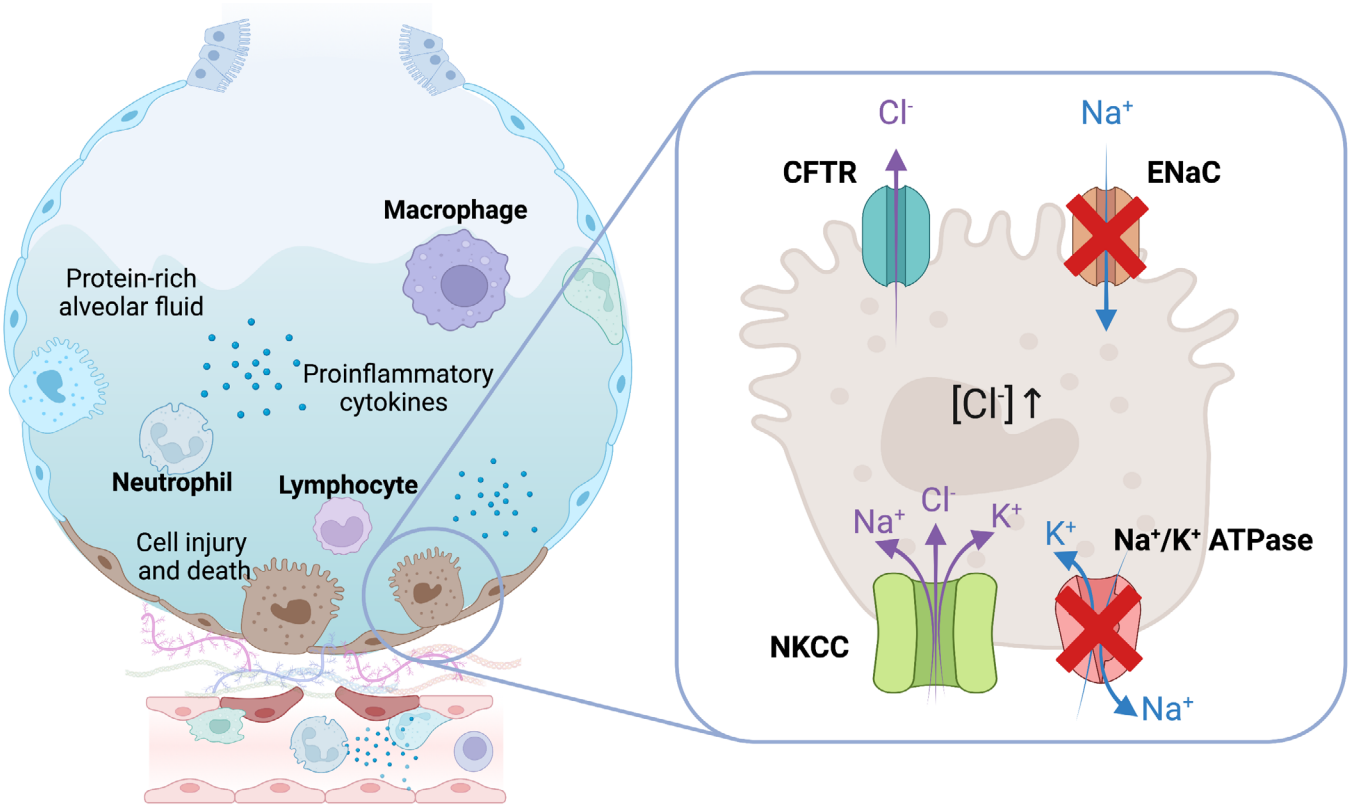

Figure 4. Schematic presentation of ion channels expressed (NKCC and CFTR) and inhibited (ENaC and Na^+/K^+ ATPase) on injured alveolar cells (both type I and type II) [21, 22]. Inflammation disrupts fluid balance through two main mechanisms: the release of vasodilators and the action of inflammatory mediators such as IL-1β, IL-8, and TNF-α. These mediators inhibit channels responsible for alveolar fluid clearance, including Na^+/K^+ ATPase, ENaC, and AQP5. Simultaneously, they increase the expression of NKCC and CFTR, which facilitate the inward transport of sodium and chloride-driven alveolar fluid secretion, respectively. CFTR: cystic #brosis transmembrane conductance regulator; ENaC: epithelial sodium channel; Na^+/K^+ ATPase: sodium/potassium ATPase pump; NKCC: Na^+-K^+-Cl^- cotransporter; Na^+: sodium, K^+: potassium, Cl^-: chloride, H_2O: water.

histology of an alveolar epithelial cell revealed cellular senescence, polymorphonuclear cell infiltration, and fibrin deposition in the interstitial and alveolar spaces [19, 97, 98]. However, it is unclear whether the observed alveolar damage directly results from the venom components, an indirect effect mediated by inflammation, or both mechanisms [99] as most evidence comes from clinical observations and the detection of surrogate biomarkers for inflammation. However, the most commonly proposed mechanism is that certain toxins, particularly those found in scorpion venom, can disrupt the delicate balance of the neuroendocrine-immune axis (discussed further in 3.3).

Cytokine storm by scorpions, snakes, insects, and spiders

Scorpion bites, notably of the genera *Tityus*, *Androctonus*, and *Buthus*, are widely recognized for their ability to trigger immune responses. [100]. Following toxin administration or bite, numerous *in vivo* studies and clinical cases have reported an elevation in proinflammatory cytokines [100] and clinical symptoms of SIRS which include severe outcomes such as cardiac and respiratory failure [101, 102]. Similar observations have been noted in *in vivo* studies and human case reviews involving venom from snakes of the genera *Crotalus* [98, 103], and *Bothrops* [104–109]. Multiple bee stings, particularly from Africanized honeybees, and *Loxosceles* spider bites can also lead to a severe envenomation syndrome characterized by the significant release of cytokines as observed in SIRS [110, 111].

Catecholamine excess

Since electrical gradient plays a crucial role in cellular physiology and neuronal communication, many venoms contain neurotoxic peptides that promote or inhibit neurotransmission, typically through voltage-gated or ligand-binding ion channels such as Na^+, K^+, Ca^{2+}, and Cl^- channels [112]. Some venomous animals, such as centipedes, spiders, scorpions, and snakes, also use the excruciating pain caused by their wounding apparatus to manipulate these channels [113].

Neuronal hyperexcitability, a state characterized by an increased level of endogenous monoamine neurotransmitters such as adrenaline, noradrenaline, acetylcholine, and dopamine, as well as other vasoactive peptides like neuropeptide-Y and endothelin-1, can lead to an "autonomic or catecholamine storm" [9]. These excessive catecholamines can induce the synthesis of pro-inflammatory mediators such as IL-6, IL-8, IL-10, and TNFs, resulting in a cytokine storm [114] that eventually

contributes to pulmonary edema. This neuroendocrine-immune axis stimulation is frequently triggered by neurotoxic substances produced by scorpions (scorpion toxins – enhance Na^+ and inhibit K^+ and Cl^- channel) [9, 101], spiders (Black widow spider – *Latrodectus* spp., Funnel-web spider – *Atrax* spp.) (latrotoxin, atracotoxin – enhance Na^+ and Ca^{2+} channel) [115, 116], and box jellyfish (Irukandji syndrome) (enhance Na^+ channel) [117]. Pulmonary edema with evidence of increased sympathetic tone and inflammation is frequently reported in cases related to these toxins [10, 117, 118].

Catecholamine storm by scorpions, spiders, centipedes, and jellyfish

Scorpion venoms are abundant in neurotoxins that commonly induce adrenergic excess. The most clinically important toxins are α-toxins that inhibit the inactivation of neuronal Na^+ channels [9], the reason behind pulmonary edema and hemorrhages (mostly fatal) in various human case reports [9, 10, 119, 120] and animal studies [121–123]. Almost all these dangerous stings are by scorpions belonging to the family Buthidae – genera *Androctonus*, *Buthus*, *Tityus*, and *Mesobuthus*, and rarely, the family Caraboctonidae – genus *Hadruroides*. Similarly, neurotoxic α-latrotoxin and atracotoxin in venoms of spiders in the genus *Latrodectus* and *Atrax*, respectively, also cause pulmonary edema in humans by dysregulating the cardiovascular system during a catecholamine storm [116, 124, 125].

A centipede bite from the genus *Scolopendra* was reported to cause cardiogenic pulmonary edema in a 19-year-old female in India. Toxin-S and other vasoactive peptides in the venoms were believed to explain cardiac global hypokinesia with generalized ST depression and hypotension [126]. The mechanism of the cardiodepressant effect was still unclear, but the toxin's ability to dysregulate ion channels can induce severe vasospasm leading to heart failure *in vivo* [127].

Irukandji syndrome, characterized by severe catecholamine surge, is marine envenomation with similar features to human case reports to those of terrestrial habitats above [43, 117]. The syndrome is commonly caused by two families of the cubozoan jellyfish: Carukiidae (including the infamous *Carukia barnesi*) and Alatinidae [128].

Hypersensitivity

Venom-induced hypersensitivity

While envenomation-induced lung injury is marked by an exaggerated inflammatory response to venoms or bites and stings that can result in pulmonary edema, hemorrhage, and ARDS, another cause of inflammation-induced lung injury is venom-induced hypersensitivity [19, 32, 90, 98]. This type of injury is depicted by severe allergic reactions to venoms and can also lead to lung inflammation and injury. Type 1 hypersensitivities, characterized by IgE-mediated mast cell degranulation, are the most common allergic reactions. These reactions release pre-formed inflammatory mediators like histamine and proteases, leading to airway constriction and pulmonary edema [129]. The well-known allergens in animal toxins are those of hymenopteran (bee or wasp) venoms where PLA_2, hyaluronidase, acid phosphatase, and dipeptidyl peptidase in honeybees, and PLA_1 and antigen-5 in Vespa are the primary allergens [130]. Severe hymenopteran venom-induced anaphylaxis commonly causes pulmonary edema [2, 131, 132] and, rarely, pulmonary hemorrhage [133, 134]. The underlying processes may include consumptive coagulopathy from inflammation, IgE-mediated effects, or direct toxic venom (melittin) interference with the complement and bradykinin pathway [135, 136].

Antivenom-induced hypersensitivity

The hypersensitivity reaction is a common acute allergic complication of antivenom therapy, and evidence suggests that the reaction might result from complement activation, immunoglobulin complex, or antivenom impurities rather than being IgE-mediated [137]. Two cases of pulmonary edema were reported in India following the administration of polyvalent F(ab')2 anti-snake venom (ASV). In Case 1, an 11-year-old child received ASV for mild local swelling after a cobra bite. After the first episode of mild allergic reactions (urticaria) subsided following adrenaline, antihistamine, and steroid, a rechallenge dose of antivenom was given. He developed hypotension and respiratory distress later confirmed to be caused by cardiogenic pulmonary edema as a side effect of the antivenom. The symptoms improved after a second dose of medications and mechanical ventilation [138]. In the second case, the patient developed severe anaphylaxis with pulmonary edema 90 minutes after ASV antivenom was given for a prolonged whole blood clotting test after a viperid bite. However, he fully recovered after supportive therapy [139].

Neurologic Involvement: Respiratory Muscle Paralysis

The respiratory muscles play a key role in the lungs to maintain their functions. Many neurotoxins can cause respiratory muscle paralysis and acute respiratory failure. However, the explicit mechanisms of neurotoxins are beyond the purview of this article. Voltage-gated channels and neuromuscular junctions are the typical targets of neurotoxins. These neurotoxins and their targets are noteworthy to mention.

Toxins that affect neuromuscular junctions can be categorized into postsynaptic and presynaptic. Postsynaptic neurotoxins bind to nicotinic acetylcholine receptors and block the action of the neurotransmitter acetylcholine. Examples of these neurotoxins include α-cobratoxin which is present in cobras (*Naja* spp.), α-bungarotoxin in kraits (*Bungarus* spp.), 3FTxs α-neurotoxin in both black mamba (*Dendroaspis polylepis*) and green mamba (*D. angusticeps*) and acanthophin-D found in common death adder (*Acanthophis antarcticus*) [140–142]. Presynaptic neurotoxins bind to nerve terminals and block the release of acetylcholine. Examples of these neurotoxins are beta bungarotoxin found in

kraits and P-elapitoxin-Aa1a in common death adder [140, 143, 144]. The victims of these snake bites typically experience muscle paralysis that progresses from small muscles to respiratory muscles and ultimately to total paralysis [145, 146].

Voltage-gated channels are located along nerve fibers and muscle cells. The opening/activation of Na^+, and Cl^- channels and the closing of the K^+ channel cause depolarization. Opening Ca^{2+} channels and depolarization activate the neurotransmitter release. While the contrary action of opening and closing these channels causes hyperpolarization and a decrease in neurotransmitter release [147]. Many toxins target voltage-gated sodium channels (VGSCs). There are 6 binding sites on VGSCs. The toxins that act on site 1 are tetrodotoxin, saxitoxin, and α-conotoxin. Tetrodotoxin can be found in many marine animals such as pufferfish (*Tetraodon* spp.), blue-ringed octopus (*Hapalochlaena lunulata*, *H. maculosa,* and *H. fasciata*), and horseshoe crab (*Carcinoscorpius rotundicauda*) [148]. Saxitoxin which resembles tetrodotoxin in structure is found in freshwater pufferfish (*Tetraodon fangi*) [149]. Alpha-conotoxins are found in some cone snails such as *Conus geographus, C. striatus,* and *C. textile* [150]. Victims will experience difficulty in limb control and paresthesia/anesthesia after consuming tetrodotoxin or saxitoxin-containing meals or being stabbed by cone snails. This could eventually lead to respiratory muscle paralysis and respiratory failure [151, 152].

Overall Clinical Presentation and Therapy

Viperid snakebites are a leading cause of envenomation-induced lung injury, likely due to the larger size of these venomous animals and their specialized venom delivery system, which can release significant amounts of venom and cause serious clinical effects [153]. Other venomous terrestrial animals, such as scorpions, spiders, and centipedes, as well as marine species, especially jellyfish, can also cause such injuries. The presence of pulmonary manifestations, such as edema, hemorrhage, exudative infiltrate, embolism, and, in rare cases, bronchospasm, often indicates poor clinical outcomes. Table 1 summarizes the toxins, animal species, and characteristics of previous human case reports or *in vivo* evidence of toxin-induced lung injury. Respiratory signs and symptoms include dyspnea, shortness of breath, tachypnea, desaturation, hemoptysis, pink frothy sputum, wheezing, rales, and crepitations. In cases of severe hypoxia, tachycardia, bradycardia, hypertension, and altered consciousness may also be present [33, 97]. Although diffuse bilateral pulmonary infiltration is more common, asymmetrical, or unilateral pulmonary injuries have also been reported [160, 161].

Table 1. Exogenous (animal) toxins with evidence of directly causing lung injury in case reports.

Animals	Toxins	Pulmonary pathology				Mechanisms	Case	Ref.
		Hmrx	Edema	Inflam.	Throm.			
Snakes								
Viperids								
	Phospholipase A_2 (VRV-PL-VIIIa)	√				Alveolar cytotoxicity		
Daboia russelli	MMP	√				Vascular damage	Humans	[14, 18, 33, 60]
	Procoagulant (cerebellar infarction)		√			Neurogenic pulmonary edema		
	Nephrotoxins		√			Renal failure		
Hypnale hypnale	Unknown hemorrhagic toxins	√				Unknown	Humans	[15, 61]
	Nephrotoxins		√			Renal failure		
Crotalus spp.	Whole venom (crotoxin, PLA_2 crotamine)	√	√	√		Inflammation, vascular damage	Mice	[19, 32, 98]
Crotalus scutulatus	Unknown				√	Procoagulant state	Humans	[83]
Agkistrodon blomhoffii ussurensis	LAOO (ABU-LAO)	√	√				Mice	[77]
Bothrops spp.	Jararhagin (P-III SVMP)	√				Inflammation, vascular damage	Humans, mice	[50, 51, 59, 105, 106, 108]
	BaP1 (P-I SVMP)							
	Aspertin (CTL) in *Bothrops asper*							
	Jararacussin-1 (serine protease) in *Bothrops jararacussu*							

Table 1. Cont.

Animals	Toxins	Pulmonary pathology				Mechanisms	Case	Ref.
		Hmrx	Edema	Inflam.	Throm.			
Bothrops lanceolatus	MMP VEGF				√	Procoagulant state	Humans	[69, 80, 81]
Vipera berus	Unknown		√			Unknown	Humans	[154]
Vipers in Morocco, Greece, and French west coast	Unknown				√	Procoagulant state	Humans	[82, 84, 85]
Bitis gabonica	Hemorrhagin		√			Vascular damage		[57, 58]
	Nephrotoxins		√			Renal failure		
Elapids								
Most elapids	Neurotoxins		√			Respiratory paralysis	Humans	[16]
Naja sputatrix	Phospholipase A_2		√	√		Inflammation (decreased fluid clearance)	Rats	[31]
Pseudonaja textilis	Cardiotoxins		√			Cardiotoxicity	Humans	[155]
Bungarus spp. (krait)	Neurotoxins, cardiotoxins		√			Cardiotoxicity, autonomic dysfunction	Humans	[156, 157]
Toads (genus *Bufo*)								
		√	√			Cardiodepressant (digitalis effect – inhibit Na^+/K^+ ATPase)	Humans, dogs	[13, 158]
Insects								
Hymenoptera	Phospholipase, Antigen-5, melittin	√	√			Inflammation, increased vascular permeability (Anaphylaxis)	Humans	[110, 131–134]
Blister beetle (genus *Epicauta*)	Cantharidin	√	√			Acantholysis	Alpacas	[45]
Spiders								
Loxosceles spp.	Phospholipase D (Sphingomyelinase D)		√			Inflammation, alveolar cytotoxicity	Humans, mice	[39, 111]
Latrodectus spp.	α-latrotoxin		√			Catecholamine storm	Humans	[116]
Atrax spp.	Atrachotoxin		√			Catecholamine storm	Humans	[124, 125]
Scorpions								
	Vasoactive peptides	√	√	√		Inflammation		
	PoTx (*Mesobuthus tumulus*)					Catecholamine storm	Humans, rats	[9, 87, 88, 96, 102]
	Neurotoxin (ex. α-toxin)							
Centipede (*Scolopendra* spp.)								
	Toxin S					Cardiotoxicity	Humans, animals	[126]
	Vasoactive peptide					Increased vascular permeability		
Jellyfish								
Nemopilema nomurai	Unspecified		√			Cytotoxicity (pore forming)	Humans, animals	[44]
Chiropsalmus quadrumanus and *C.quadrigatus*	Unspecified		√			Cardiotoxicity	Humans	[159, 163]

Table 1. Cont.

Animals	Toxins	Pulmonary pathology				Mechanisms	Case	Ref.
		Hmrx	Edema	Inflam.	Throm.			
Chironex fleckeri	Unspecified		√			Cardiotoxicity	Humans	[164]
Irukandji jellyfish (ex. *Carukia* spp.)	Unspecified		√			Irukandji syndrome	Humans	[117]
Stonefish (family Synaceia)								
	Unspecified	√	√	√		Inflammation Alveolar cytotoxicity	Humans, animals	[41]
Sea anemone								
Actinia equina	Equinatoxin II		√			Increased vascular permeability	Animals	[165]

Abbreviation: Hmrx – hemorrhage; Inflam. – inflammation; LAOO – L-amino acid oxidases; MMP – matrix metalloproteinase; N/A – not available; PoTx – pulmonary edema-producing toxin; RVBCMP – Russell's viper basic coagulant metalloproteinase; SVMP – snake venom metalloproteinase; Throm. – thrombosis; VEGF – vascular endothelial growth factor; VRV-PL-VIIIa – *Vipera russelli* venom phospholipase A_2 fraction VIIIa

Lung damage occurs nearly immediately at the cellular level [19], but clinical signs may be immediate (within minutes to hours) or delayed (days) depending on the mechanisms. Although anaphylaxis occurs acutely (a few minutes), significant sequelae such as pulmonary edema and, less frequently, bleeding, can take longer (a few hours) [131–134]. Prothrombotic actions may take a few hours to cause pulmonary embolism [69]. Pulmonary edema or ARDS from sympathetic overactivity is more immediate (minutes to hours) when compared to the process of excessive inflammation and subsequent multiorgan failure, which may take days [44, 97, 117, 126, 162]. Pulmonary hemorrhage can occur at any time from a few hours [30, 50, 59, 60] to many days, and is often accompanied by systemic coagulopathy [33, 62].

The main treatment for envenomation-induced lung injury is still airway and breathing support therapy. Adrenaline, steroids, and antihistamines are specifically used to treat pulmonary edema or bronchospasm caused by anaphylaxis. Only antivenoms are used as specific antidotes in human case reports. Blood components and antivenoms are frequently provided to patients who experience pulmonary hemorrhage, with varying degrees of success [33, 60, 62]. Supporting the primary target organ is the main goal of treatment for pulmonary edema caused by cardiotoxins or neurotoxins.

Conclusion

Animal toxins can inflict severe damage to the respiratory system of the host, resulting in various pulmonary manifestations, including but not limited to edema, hemorrhage, or embolism. These serious complications of envenomation require prompt and effective management, as they have the potential to result in unfavorable clinical outcomes. Therefore, understanding the mechanisms underlying toxin-induced lung injury and developing efficacious treatment modalities are imperative for enhancing patient outcomes and reducing the associated mortality rates linked to envenomation.

Acknowledgment

Figures in this manuscript were created with BioRender.com.

Availability of data and materials

Not applicable

Funding

The authors declare no funding for this study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ST conceived the structure and detail of the manuscript. ST and SS wrote the paper and participated in the revisions of it. SS and VS revised the paper. All authors read and approved the final manuscript.

Ethics approval

Not applicable

Consent for publication

Not applicable

References

1. Zhang Y. Why do we study animal toxins? Dongwuxue Yanjiu. 2015 Jul;36(4):183-222.
2. Ryan RYM, Seymour J, Loukas A, Lopez JA, Ikonomopoulou MP, Miles JJ. Immunological responses to envenomation. Front Immunol. 2021;12.
3. Chen N, Xu S, Zhang Y, Wang F. Animal protein toxins: origins and therapeutic applications. Biophys Rep. 2018;4(5):233-42.
4. Herzig V, Cristofori-Armstrong B, Israel MR, Nixon SA, Vetter I, King GF. Animal toxins – Nature's evolutionary-refined toolkit for basic research and drug discovery. Biochem Pharmacol. 2020;181:114096.

5. Casewell NR, Wuster W, Vonk FJ, Harrison RA, Fry BG. Complex cocktails: the evolutionary novelty of venoms. Trends Ecol Evol. 2013;28(4):219-29.
6. D'Ambra I, Lauritano C. A review of toxins from cnidaria. Mar Drugs. 2020;18(10):507.
7. Helden DFV, Dosen PJ, O'Leary MA, Isbister GK. Two pathways for venom toxin entry consequent to injection of an Australian elapid snake venom. Sci Rep. 2019;9(1):8595.
8. Arbuckle K. Evolutionary context of venom in animals. In: Malhotra A, Gopalakrishnakone P, editors. Evolution of venomous animals and their toxins. Dordrecht: Springer Netherlands; 2017. p. 3-31.
9. Isbister GK, Bawaskar HS. Scorpion envenomation. N Engl J Med. 2014;371(5):457-63.
10. Bahloul M, Chaari A, Dammak H, Samet M, Chtara K, Chelly H, Hamida CB, Kallel H, Bouaziz M. Pulmonary edema following scorpion envenomation: Mechanisms, clinical manifestations, diagnosis, and treatment. Int J Cardiol. 2013;162(2):86-91.
11. Pneumatikos IA, Galiatsou E, Goe D, Kitsakos A, Nakos G, Vougiouklakis TG. Acute fatal toxic myocarditis after black widow spider envenomation. Ann Emerg Med. 2003;41(1):158.
12. John Binu A, Kumar Mishra A, Gunasekaran K, Iyadurai R. Cardiovascular manifestations and patient outcomes following snake envenomation: a pilot study. Trop Doct. 2019;49(1):10-3.
13. Ashok G, Ramkumar, Sakunthala SR, Rajasekaran D. An interesting case of cardiotoxicity due to bufotoxin (toad toxin). J Assoc Physicians India. 2011;59:737-8.
14. Jeyarajah R. Russell's viper bite in Sri Lanka. A study of 22 cases. Am J Trop Med Hyg. 1984;33(3):506-10.
15. Joseph JK, Simpson ID, Menon NC, Jose MP, Kulkarni KJ, Raghavendra GB, Warrell DA. First authenticated cases of life-threatening envenoming by the hump-nosed pit viper (*Hypnale hypnale)* in India. Trans R Soc Trop Med Hyg. 2007;101(1):85-90.
16. Gnanathasan A, Rodrigo C. Pulmonary effects and complications of snakebites. Chest. 2014;146(5):1403-12.
17. Halford ZA, Yu PY, Likeman RK, Hawley-Molloy JS, Thomas C, Bingham JP. Cone shell envenomation: epidemiology, pharmacology and medical care. Diving Hyperb Med. 2015;45(3):200-7.
18. Gupta S, Tewari A, Nair V. Cerebellar infarct with neurogenic pulmonary edema following viper bite. J Neurosci Rural Pract. 2012;3(1):74-6.
19. Oliveira Neto J, Silveira JAM, Serra DS, Viana DA, Borges-Nojosa DM, Sampaio CMS, Monteiro HSA, Cavalcante FSA, Evangelista JSAM. Pulmonary mechanic and lung histology induced by *Crotalus durissus cascavella* snake venom. Toxicon. 2017;137:144-9.
20. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG, Calfee CS. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019;5(1):1-22.
21. Huppert LA, Matthay MA, Ware LB. Pathogenesis of acute respiratory distress syndrome. Semin Respir Crit Care Med. 2019;40(1):31-9.
22. Weidenfeld S, Kuebler WM. Cytokine-regulation of Na^+-K^+-Cl^- cotransporter 1 and cystic fibrosis transmembrane conductance regulator-potential role in pulmonary inflammation and edema formation. Front Immunol. 2017;8:393.
23. Davey A, McAuley DF, O'Kane CM. Matrix metalloproteinases in acute lung injury: mediators of injury and drivers of repair. Eur Respir J. 2011;38(4):959-70.
24. Lahiani A, Yavin E, Lazarovici P. The molecular basis of toxins' interactions with intracellular signaling via discrete portals. Toxins (Basel). 2017;9(3):E107.
25. Gasanov SE, Dagda RK, Rael ED. Snake venom cytotoxins, phospholipase A_2s, and Zn^{2+}-dependent metalloproteinases: Mechanisms of action and pharmacological relevance. J Clin Toxicol. 2014;4(1):1000181.
26. Clark GC, Casewell NR, Elliott CT, Harvey AL, Jamieson AG, Strong PN, et al. Friends or foes? Emerging impacts of biological toxins. Trends Biochem Sci. 2019;44(4):365-79.
27. Rádis-Baptista G. Cell-penetrating peptides derived from animal venoms and toxins. Toxins (Basel). 2021;13(2):147.
28. Fry BG. From genome to "venome": molecular origin and evolution of the snake venom proteome inferred from phylogenetic analysis of toxin sequences and related body proteins. Genome Res. 2005;15(3):403-20.
29. Lomonte B, Križaj I. Snake venom phospholipase A_2 toxins. Handbook of Venoms and Toxins of Reptiles: CRC Press; 2021. p. 389-412.
30. Uma B, Veerabasappa Gowda T. Molecular mechanism of lung hemorrhage induction by VRV-PL-VIIIa from Russell's viper (*Vipera russelli*) venom. Toxicon. 2000;38(8):1129-47.
31. Cher CDN, Armugam A, Lachumanan R, Coghlan M-W, Jeyaseelan K. Pulmonary inflammation and edema induced by phospholipase A_2: global gene analysis and effects on aquaporins and Na^+/K^+-ATPase. J Biol Chem. 2003;278(33):31352-60.
32. Nonaka PN, Amorim CF, Paneque Peres AC, E Silva CAM, Zamuner SR, Ribeiro W, Cogo JC, Vieira RP, Dolhnikoff M, Oliveira LVF. Pulmonary mechanic and lung histology injury induced by *Crotalus durissus terrificus* snake venom. Toxicon. 2008 Jun 1;51(7):1158-66.
33. Palangasinghe DR, Weerakkody RM, Dalpatadu CG, Gnanathasan CA. A fatal outcome due to pulmonary hemorrhage following Russell's viper bite. Saudi Med J. 2015;36(5):634-7.
34. Sampley S, Sakhuja V, Bhasin D, Singh K, Singh H. Plasmapheresis for pulmonary hemorrhage following viperine snakebite: A case report with review of literature. Indian J Crit Care Med. 2020;24(10):986-90.
35. Konshina AG, Boldyrev IA, Utkin YN, Omel'kov AV, Efremov RG. Snake cytotoxins bind to membranes via interactions with phosphatidylserine head groups of lipids. PLoS One. 2011;6(4):e19064.
36. Pucca MB, Ahmadi S, Cerni FA, Ledsgaard L, Sørensen CV, McGeoghan FTS, Stewart T, Schoof E, Lomonte B, auf dem Keller U, Arantes EC, Caliskan F, Lausten AH. Unity makes strength: Exploring intraspecies and interspecies toxin synergism between phospholipases A_2 and cytotoxins. Front Pharmacol. 2020;11:611.
37. Neundorf I. Antimicrobial and cell-penetrating peptides: How to understand two distinct functions despite similar physicochemical properties. Adv Exp Med Biol. 2019;1117:93-109.
38. Šuput D. Equinatoxins: A review. In: Gopalakrishnakone P, editor. Marine and freshwater toxins: Marine and freshwater toxins. Dordrecht: Springer Netherlands; 2021. p. 1-17.
39. Thompson AL. Laboratory testing in monitoring the effects of brown recluse spider bites. Lab Med. 2013;44(4):300-3.
40. Rivera IG, Ordonez M, Presa N, Gomez-Larrauri A, Simon J, Trueba M, Gomez-Muñoz A. Sphingomyelinase D/ceramide 1-phosphate in cell survival and inflammation. Toxins (Basel). 2015;7(5):1457-66.
41. Maillaud C, Hoang-Oppermann T, Hoang-Oppermann V, Rigot H, Girardot S, Nour M. Is stonefish *Synanceia verrucosa* envenomation potentially lethal? Toxicon. 2020;184:78-82.
42. Campos FV, Menezes TN, Malacarne PF, Costa FL, Naumann GB, Gomes HL, Figueiredo SG. A review on the *Scorpaena plumieri* fish venom and its bioactive compounds. J Venom Anim Toxins incl Trop Dis. 2016;22:35. Epub 20161221. doi: 10.1186/s40409-016-0090-7.
43. Cunha SA, Dinis-Oliveira RJ. Raising awareness on the clinical and forensic aspects of jellyfish stings: A worldwide increasing threat. Int J Environ Res Public Health. 2022;19(14).
44. Kim JH, Han SB, Durey A. Fatal pulmonary edema in a child after jellyfish stings in Korea. Wilderness Environ Med. 2018;29(4):527-30.
45. Simpson KM, Streeter RN, De Souza P, Genova SG, Morgan SE. Cantharidin toxicosis in 2 alpacas. Can Vet J. 2013;54(5):456-62.
46. Sharp C, Millar AB, Medford ARL. Advances in understanding of the pathogenesis of acute respiratory distress syndrome. Respiration. 2015;89(5):420-34.
47. Gutiérrez J, Escalante T, Rucavado A, Herrera C, Fox J. A comprehensive view of the structural and functional alterations of extracellular matrix by snake venom metalloproteinases (SVMP): Novel perspectives on the pathophysiology of envenoming. Toxins (Basel). 2016;8(10):304.
48. Castro AC, Escalante T, Rucavado A, Gutiérrez JM. Basement membrane degradation and inflammation play a role in the pulmonary hemorrhage induced by a P-III snake venom metalloproteinase. Toxicon. 2021;197:12-23.

49. Slagboom J, Kool J, Harrison RA, Casewell NR. Haemotoxic snake venoms: their functional activity, impact on snakebite victims and pharmaceutical promise. Br J Haematol. 2017;177(6):947-59.
50. Escalante T, Núñez J, Moura da Silva AM, Rucavado A, Theakston RDG, Gutiérrez JM. Pulmonary hemorrhage induced by jararhagin, a metalloproteinase from *Bothrops jararaca* snake venom. Toxicol Appl Pharmacol. 2003;193(1):17-28.
51. Rucavado A, Soto M, Escalante T, Loría GD, Arni R, Gutiérrez JM. Thrombocytopenia and platelet hypoaggregation induced by *Bothrops asper* snake venom. Toxins involved and their contribution to metalloproteinase-induced pulmonary hemorrhage. Thromb Haemost. 2005;94(1):123-31.
52. Silveira KS, Boechem NT, do Nascimento SM, Murakami YL, Barboza AP, Melo PA, Castro P, Moraes VLG, Rocco PRM, Zin WA. Pulmonary mechanics and lung histology in acute lung injury induced by *Bothrops jararaca* venom. Respir Physiol Neurobiol. 2004;139(2):167-77.
53. Ayvazyan N, Ghukasyan G, Ghulikyan L, Kirakosyan G, Sevoyan G, Voskanyan A, Karabekyan Z. The Contribution of Phospholipase A(2) and Metalloproteinases to the Synergistic Action of Viper Venom on the Bioenergetic Profile of Vero Cells. Toxins (Basel). 2022;14(11).
54. Bustillo S, Gay CC, Garcia Denegri ME, Ponce-Soto LA, Bal de Kier Joffe E, Acosta O, Leiva LC. Synergism between baltergin metalloproteinase and Ba SPII RP4 PLA_2 from *Bothrops alternatus* venom on skeletal muscle (C2C12) cells. Toxicon. 2012 Feb;59(2):338-43.
55. Bustillo S, Garcia-Denegri ME, Gay C, Van de Velde AC, Acosta O, Angulo Y, Lomonte B, Gutiérrez JM, Leiva L. Phospholipase A(2) enhances the endothelial cell detachment effect of a snake venom metalloproteinase in the absence of catalysis. Chem Biol Interact. 2015 Oct 5;240:30-6.
56. Silva A, Gunawardena P, Weilgama D, Maduwage K, Gawarammana I. Comparative in-vivo toxicity of venoms from South Asian hump-nosed pit vipers (Viperidae: Crotalinae: *Hypnale*). BMC Res Notes. 2012;5:471.
57. Marsh N, Gattullo D, Pagliaro P, Losano G. The Gaboon viper, *Bitis gabonica*: hemorrhagic, metabolic, cardiovascular and clinical effects of the venom. Life Sci. 1997;61(8):763-9.
58. Marsh NA, Whaler BC. The Gaboon viper (*Bitis gabonica*): Its biology, venom components and toxinology. Toxicon. 1984;22(5):669-94.
59. Benvenuti LA, França FOS, Barbaro KC, Nunes JR, Cardoso JLC. Pulmonary haemorrhage causing rapid death after *Bothrops jararacussu* snakebite: a case report. Toxicon. 2003;42(3):331-4.
60. Rathnayaka RMMKN, Ranathunga P, Kularathna SAM. Pulmonary haemorrhage following Russell's viper (*Daboia russelii*) envenoming in Sri Lanka. Asia Pac J Med Toxicol. 2020;9:72-6.
61. Srirangan A, Pushpakumara J, Wanigasuriya K. A life-threatening complication due to pulmonary haemorrhage following hump-nosed viper bite. BMC Pulm Med. 2020;20(1):35.
62. Rathnayaka RMMKN, Ranathunga PEAN, Kularatne SaM. Systemic bleeding including pulmonary haemorrhage following hump-nosed pit viper (*Hypnale hypnale*) envenoming: A case report from Sri Lanka. Toxicon. 2019;170:21-8.
63. Namal Rathnayaka R, Nishanthi Ranathunga PEA, Kularatne SAM. Sudden death following hump-nosed pit viper (*Hypnale hypnale*) bite. Wilderness Environ Med. 2021;32(1):125-7.
64. Kemparaju K, Girish KS. Snake venom hyaluronidase: a therapeutic target. Cell Biochem Funct. 2006;24(1):7-12.
65. Khan N, Niazi ZR, Rehman FU, Akhtar A, Khan MM, Khan S, Baloch N, Khan S. Hyaluronidases: A therapeutic enzyme. Protein Pept Lett. 2018;25(7):663-76.
66. Bordon KC, Wiezel GA, Amorim FG, Arantes EC. Arthropod venom Hyaluronidases: biochemical properties and potential applications in medicine and biotechnology. J Venom Anim Toxins incl Trop Dis. 2015;21:43. Epub 20151022. doi: 10.1186/s40409-015-0042-7.
67. Arruda Macedo JK, Fox JW, de Souza Castro M. Disintegrins from snake venoms and their applications in cancer research and therapy. Curr Protein Peptide Sci. 2015;16(6):532-48.
68. Plosa EJ, Benjamin JT, Sucre JM, Gulleman PM, Gleaves LA, Han W, Kook S, Polosukhin VV, Haake SM, Guttentag SH, Young LR, Pozzi A, Blackwell TS, Zent R. β1 Integrin regulates adult lung alveolar epithelial cell inflammation. JCI Insight. 2020;5(2):e129259.
69. Estrade G, Garnier D, Bernasconi F, Donatien Y. Pulmonary embolism and disseminated intravascular coagulation after being bitten by a *Bothrops lanceolatus* snake. Apropos of a case. Arch Mal Coeur Vaiss. 1989;82(11):1903-5.
70. Berling I, Isbister GK. Hematologic effects and complications of snake envenoming. Transfus Med Rev. 2015;29(2):82-9.
71. Kini RM, Koh CY. Metalloproteases affecting blood coagulation, fibrinolysis and platelet aggregation from snake venoms: Definition and nomenclature of interaction sites. Toxins (Basel). 2016;8(10):284.
72. Patel S. A critical review on serine protease: Key immune manipulator and pathology mediator. Allergol Immunopathol (Madr). 2017;45(6):579-91.
73. Markland FS. Snake venoms and the hemostatic system. Toxicon. 1998;36(12):1749-800.
74. Kang TS, Georgieva D, Genov N, Murakami MT, Sinha M, Kumar RP, Kaur P, Kumar S, Dey S, Sharma S, Vrielink A, Betzel C, Takeda S, Arni RK, Singh TP, Kini RM. Enzymatic toxins from snake venom: structural characterization and mechanism of catalysis. FEBS J. 2011 Dec;278(23):4544-76.
75. Arlinghaus FT, Eble JA. C-type lectin-like proteins from snake venoms. Toxicon. 2012;60(4):512-9.
76. Kini RM. Anticoagulant proteins from snake venoms: structure, function and mechanism. Biochem J. 2006;397(3):377-87.
77. Wei XL, Wei JF, Li T, Qiao LY, Liu YL, Huang T, He SH. Purification, characterization and potent lung lesion activity of an L-amino acid oxidase from *Agkistrodon blomhoffii ussurensis* snake venom. Toxicon. 2007;50(8):1126-39.
78. Bhattacharjee P, Mitra J, Bhattacharyya D. L-amino acid oxidase from venoms. 2017. p. 295-320.
79. Nielsen VG. Characterization of L-amino acid oxidase derived from *Crotalus adamanteus* venom: Procoagulant and anticoagulant activities. Int J Mol Sci. 2019;20(19):4853.
80. Thomas L, Tyburn B, Bucher B, Pecout F, Ketterle J, Rieux D, Smadja D, Garnier D, Plumelle Y. Prevention of thromboses in human patients with *Bothrops lanceolatus* envenoming in Martinique: failure of anticoagulants and efficacy of a monospecific antivenom. Research Group on Snake Bites in Martinique. Am J Trop Med Hyg. 1995 May;52(5):419-26.
81. Malbranque S, Piercecchi-Marti MD, Thomas L, Barbey C, Courcier D, Bucher B, Smadja DS, Warrell DA. Fatal diffuse thrombotic microangiopathy after a bite by the "Fer-de-Lance" pit viper (*Bothrops lanceolatus*) of Martinique. Am J Trop Med Hyg. 2008 Jun;78(6):856-61.
82. Bart G, Pineau S, Biron C, Connault J, Artifoni M. Bilateral pulmonary embolism following a viper envenomation in France: A case report and review. Medicine (Baltimore). 2016;95(19):e2798.
83. Bhagat R, Sharma K, Sarode R, Shen YM. Delayed massive pulmonary thromboembolic phenomenon following envenomation by Mojave rattlesnake (*Crotalus scutulatus*). Thromb Haemost. 2010;104(1):186-8.
84. Chani M, L'Kassimi H, Abouzahir A, Nazi M, Mion G. [Three case-reports of viperin envenoming in Morocco]. Ann Fr Anesth Reanim. 2008;27(4):330-4.
85. Makis A, Kattamis A, Grammeniatis V, Sihlimiri P, Kotsonis H, Iliadis A, Siamopoulou A, Chaliasos N. Pulmonary embolism after snake bite in a child with Diamond-Blackfan anemia. J Pediatr Hematol Oncol. 2011;33(1):68-70.
86. Lameu C, Neiva M, F. Hayashi MA. Venom bradykinin-related peptides (BRPs) and its multiple biological roles. In: Radis-Baptista G, editor. An Integrated View of the Molecular Recognition and Toxinology – From Analytical Procedures to Biomedical Applications: InTech; 2013.
87. Deshpande SB, Akella A. Non-cardiogenic mechanisms for the pulmonary edema induced by scorpion venom. Int J Cardiol. 2012;157(3):426-7.
88. Deshpande SB, Alex AB, Jagannadham MV, Rao GR, Tiwari AK. Identification of a novel pulmonary oedema-producing toxin from Indian red scorpion (*Mesobuthus tamulus*) venom. Toxicon. 2005;45(6):735-43.
89. Yang CY, Chen CS, Yiang GT, Cheng YL, Yong SB, Wu MY, Li CJ. New insights into the immune molecular regulation of the pathogenesis of acute respiratory distress syndrome. Int J Mol Sci. 2018;19(2).
90. Rucavado A, Nicolau CA, Escalante T, Kim J, Herrera C, Gutiérrez JM, Fox JW. Viperid envenomation wound exudate contributes to increased

vascular permeability via a DAMPS/TLR-4 mediated pathway. Toxins (Basel). 2016;8(12):E349.

91. Chambers RC. Procoagulant signaling mechanisms in lung inflammation and fibrosis: novel opportunities for pharmacological intervention? Br J Pharmacol. 2008;153 Suppl 1(Suppl 1):S367-78.
92. Voronov E, Apte RN, Sofer S. The systemic inflammatory response syndrome related to the release of cytokines following severe envenomation. J Venom Anim Toxins. 1999;5(1). doi: 10.1590/S0104-79301999000100002.
93. Jarczak D, Nierhaus A. Cytokine storm-Definition, causes, and implications. Int J Mol Sci. 2022;23(19).
94. Paolino G, Di Nicola MR. Letter to the Editor: Acute-phase response fever in Viperidae as a potential and additional clinical sign. Toxicon. 2020;184:229-30.
95. Chakraborty RK, Burns B. Systemic inflammatory response syndrome. StatPearls. Treasure Island (FL) 2023.
96. Petricevich VL. Cytokine and nitric oxide production following severe envenomation. Curr Drug Targets Inflamm Allergy. 2004;3(3):325-32.
97. Amaral CFS, Barbosa AJ, Leite VHR, Tafuri WL, de Rezende NA. Scorpion sting-induced pulmonary oedema: Evidence of increased alveolocapillary membrane permeability. Toxicon. 1994;32(8):999-1003.
98. Azevedo E, Figueiredo RG, Pinto RV, Ramos TdCF, Sampaio GP, Bulhosa Santos RP, Guerreiro MLS, Biondi I, Trindade SC. Evaluation of systemic inflammatory response and lung injury induced by *Crotalus durissus cascavella* venom. PLoS One. 2020;15(2):e0224584.
99. Issaad N, Ait-Lounis A, Laraba-Djebari F. Cytotoxicity and actin cytoskeleton damage induced in human alveolar epithelial cells by *Androctonus australis hector* venom. Toxin Rev. 2018;37(1):67-74.
100. Reis MB, Zoccal KF, Gardinassi LG, Faccioli LH. Scorpion envenomation and inflammation: Beyond neurotoxic effects. Toxicon. 2019;167:174-9.
101. Petricevich VL. Scorpion venom and the inflammatory response. Mediators Inflamm. 2010;2010:903295.
102. Fukuhara YD, Reis ML, Dellalibera-Joviliano R, Cunha FQ, Donadi EA. Increased plasma levels of IL-1beta, IL-6, IL-8, IL-10 and TNF-alpha in patients moderately or severely envenomed by *Tityus serrulatus* scorpion sting. Toxicon. 2003;41(1):49-55.
103. Hernandez Cruz A, Garcia-Jimenez S, Zucatelli Mendonca R, Petricevich VL. Pro- and anti-inflammatory cytokines release in mice injected with *Crotalus durissus terrificus* venom. Mediators Inflamm. 2008;2008:874962.
104. Barros SF, Friedlanskaia I, Petricevich VL, Kipnis TL. Local inflammation, lethality and cytokine release in mice injected with *Bothrops atrox* venom. Mediators Inflamm. 1998;7(5):339-46.
105. Petricevich VL, Teixeira CF, Tambourgi DV, Gutierrez JM. Increments in serum cytokine and nitric oxide levels in mice injected with *Bothrops asper* and *Bothrops jararaca* snake venoms. Toxicon. 2000;38(9):1253-66.
106. Zamuner SR, Gutierrez JM, Muscara MN, Teixeira SA, Teixeira CF. *Bothrops asper* and *Bothrops jararaca* snake venoms trigger microbicidal functions of peritoneal leukocytes *in vivo*. Toxicon. 2001;39(10):1505-13.
107. Zamuner SR, Zuliani JP, Fernandes CM, Gutierrez JM, de Fatima Pereira Teixeira C. Inflammation induced by *Bothrops asper* venom: release of proinflammatory cytokines and eicosanoids, and role of adhesion molecules in leukocyte infiltration. Toxicon. 2005;46(7):806-13.
108. Lomonte B, Tarkowski A, Hanson LA. Host response to *Bothrops asper* snake venom. Analysis of edema formation, inflammatory cells, and cytokine release in a mouse model. Inflammation. 1993;17(2):93-105.
109. Barraviera B, Lomonte B, Tarkowski A, Hanson LÅ, Meira DA. Acute-phase reactions, including cytokines, in patients bitten by *Bothrops* and *Crotalus* snakes in Brazil. J Venom Anim Toxins incl Trop Dis. 1995;1(1). doi: 10.1590/S0104-79301995000100003.
110. Ferreira Jr RS, Almeida RA, Barraviera SR, Barraviera B. Historical perspective and human consequences of Africanized bee stings in the Americas. J Toxicol Environ Health B Crit Rev. 2012;15(2):97-108.
111. Tambourgi DV, Petricevich VL, Magnoli FC, Assaf SL, Jancar S, Dias Da Silva W. Endotoxemic-like shock induced by *Loxosceles* spider venoms: pathological changes and putative cytokine mediators. Toxicon. 1998;36(2):391-403.
112. Utkin Y, Vassilevski A, Kudryavtsev D, Undheim EAB. Editorial: Animal toxins as comprehensive pharmacological tools to identify diverse ion channels. Front Pharmacol. 2019;10:423.
113. Ombati R, Luo L, Yang S, Lai R. Centipede envenomation: Clinical importance and the underlying molecular mechanisms. Toxicon. 2018;154:60-8.
114. Staedtke V, Bai RY, Kim K, Darvas M, Davila ML, Riggins GJ, Rothman PB, Papadopoulos N, Kinzler KW, Vogelstein B, Zhou S. Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. Nature. 2018;564(7735):273-7.
115. Nicholson GM, Graudins A. Spiders of medical importance in the Asia-Pacific: atracotoxin, latrotoxin, and related spider neurotoxins. Clin Exp Pharmacol Physiol. 2002;29(9):785-94.
116. Caruso MB, Lauria PSS, de Souza CMV, Casais ESLL, Zingali RB. Widow spiders in the New World: a review on *Latrodectus Walckenaer*, 1805 (Theridiidae) and latrodectism in the Americas. J Venom Anim Toxins incl Trop Dis. 2021;27:e20210011. Epub 20211022. doi: 10.1590/1678-9199-JVATITD-2021-0011.
117. Nickson CP, Waugh EB, Jacups SP, Currie BJ. Irukandji syndrome case series from Australia's tropical northern territory. Ann Emerg Med. 2009;54(3):395-403.
118. Ismail M, Asaad N, Suwaidi JA, Kawari MA, Salam A. Acute myocarditis and pulmonary edema due to scorpion sting. Glob Cardiol Sci Pract. 2016;2016(1):e201610.
119. Feola A, Perrone MA, Piscopo A, Casella F, Della Pietra B, Di Mizio G. Autopsy findings in case of fatal scorpion sting: A systematic review of the literature. Healthcare (Basel). 2020;8(3).
120. Cupo P. Clinical update on scorpion envenoming. Rev Soc Bras Med Trop. 2015;48(6):642-9.
121. Zayerzadeh E, Koohi MK, Zare Mirakabadi A, Purkabireh M, Kassaaian SE, Rabbani SH, Anvari MS, Boroumand MA, Sadeghian S. Cardiopulmonary complications induced by Iranian *Mesobuthus eupeus* scorpion venom in anesthetized rabbits. J Venom Anim Toxins ncl Trop Dis. 2010;16(1):46-59.
122. Costal-Oliveira F, Guerra-Duarte C, Oliveira MS, Castro KLPd, Lopes-de-Sousa L, Lara A, Gomes ERM, Bonilla C, Guatimosim S, Melo MM, Chávez-Olórtegui C. Cardiorespiratory alterations in rodents experimentally envenomed with *Hadruroides lunatus* scorpion venom. J Venom Anim Toxins incl Trop Dis. 2016 Jul 15;23(1):2.
123. Paneque Peres AC, Nonaka PN, de Carvalho Pde T, Toyama MH, Silva CA, Vieira RP, Dolhnikoff M, Zamuner SR, Oliveira LVF. Effects of *Tityus serrulatus* scorpion venom on lung mechanics and inflammation in mice. Toxicon. 2009;53(7-8):779-85.
124. Isbister GK, Warner G. Acute myocardial injury caused by Sydney funnel-web spider (*Atrax robustus*) envenoming. Anaesth Intensive Care. 2003;31(6):672-4.
125. Isbister GK, Sellors KV, Beckmann U, Chiew AL, Downes MA, Berling I. Catecholamine-induced cardiomyopathy resulting from life-threatening funnel-web spider envenoming. Med J Aust. 2015;203(7):302-4.
126. Kartik M, Haranath SP, Amte R, Gopal P. Shock and pain: Centipede bite causing reversible myocardial injury. Chest. 2012;142(4):321A.
127. Chu Y, Qiu P, Yu R. Centipede venom peptides acting on ion channels. Toxins (Basel). 2020;12(4).
128. Gershwin LA, Richardson AJ, Winkel KD, Fenner PJ, Lippmann J, Hore R, Avila-Soria G, Brewer D, Kloser RJ, Steven A, Condie S. Biology and ecology of Irukandji jellyfish (Cnidaria: Cubozoa). Adv Mar Biol. 2013;66:1-85.
129. Nguyen SMT, Rupprecht CP, Haque A, Pattanaik D, Yusin J, Krishnaswamy G. Mechanisms governing anaphylaxis: Inflammatory cells, mediators, endothelial gap junctions and beyond. Int J Mol Sci. 2021;22(15):7785.
130. Pesek RD, Lockey RF. Management of insect sting hypersensitivity: an update. Allergy Asthma Immunol Res. 2013;5(3):129-37.
131. Kularatne K, Kannangare T, Jayasena A, Jayasekera A, Waduge R, Weerakoon K, Kularatne SAM. Fatal acute pulmonary oedema and acute renal failure following multiple wasp/hornet (*Vespa affinis*) stings in Sri Lanka: two case reports. J Med Case Reports. 2014;8:188.

132. Sharmila RR, Chetan G, Narayanan P, Srinivasan S. Multiple organ dysfunction syndrome following single wasp sting. Indian J Pediatr. 2007;74(12):1111-2.
133. Lam SM. Acute pulmonary hemorrhage following a honeybee sting: a case report. J Microbiol Immunol Infect. 1998;31(2):133-6.
134. Mukhopadhyay A, Fong KY, Lim TK. Diffuse alveolar haemorrhage: A rare reaction to insect sting. Respirology. 2002;7(2):157-9.
135. Mingomataj EÇ, Bakiri AH, Ibranji A, Sturm GJ. Unusual reactions to Hymenoptera stings: What should we keep in mind? Clin Rev Allergy Immunol. 2014;47(1):91-9.
136. Mingomataj EC, Bakiri AH. Episodic hemorrhage during honeybee venom anaphylaxis: potential mechanisms. J Investig Allergol Clin Immunol. 2012;22(4):237-44.
137. de Silva HA, Ryan NM, de Silva HJ. Adverse reactions to snake antivenom, and their prevention and treatment: Adverse reactions to snake antivenom, and their prevention and treatment. Br J Clin Pharmacol. 2016;81(3):446-52.
138. Singh A, Biswal N, Nalini P, Sethuraman, Badhe A. Acute pulmonary edema as a complication of anti-snake venom therapy. Indian J Pediatr. 2001;68(1):81-2.
139. Bhol KK, Ray S. Non cardiogenic pulmonary edema in a case of viperidine snake bite. J Mar Med Soc. 2016;18:51.
140. Zhou K, Luo W, Liu T, Ni Y, Qin Z. Neurotoxins acting at synaptic sites: A brief review on mechanisms and clinical applications. Toxins (Basel). 2022;15(1).
141. Ainsworth S, Petras D, Engmark M, Sussmuth RD, Whiteley G, Albulescu LO, Kazandjian TD, Wagstaff SC, Rowley P, Wuster W, Dorrestein PC, Arias AS, Gutiérrez JM, Harrison RA, Casewell NR, Calvete JJ. The medical threat of mamba envenoming in sub-Saharan Africa revealed by genus-wide analysis of venom composition, toxicity and antivenomics profiling of available antivenoms. J Proteomics. 2018;172:173-89.
142. Sheumack DD, Spence I, Tyler MI, Howden ME. The complete amino acid sequence of a post-synaptic neurotoxin isolated from the venom of the Australian death adder snake *Acanthophis antarcticus*. Comp Biochem Physiol B. 1990;95(1):45-50.
143. Rugolo M, Dolly JO, Nicholls DG. The mechanism of action of beta-bungarotoxin at the presynaptic plasma membrane. Biochem J. 1986;233(2):519-23.
144. Blacklow B, Escoubas P, Nicholson GM. Characterization of the heterotrimeric presynaptic phospholipase A_2 neurotoxin complex from the venom of the common death adder (*Acanthophis antarcticus*). Biochem Pharmacol. 2010;80(2):277-87.
145. Chanhome L, Cox MJ, Wilde H, Jintakoon P, Chaiyabutr N, Sitprija V. Venomous snakebite in Thailand. I: Medically important snakes. Mil Med. 1998;163(5):310-7.
146. Pe T, Myint T, Htut A, Htut T, Myint AA, Aung NN. Envenoming by Chinese krait (*Bungarus multicinctus*) and banded krait (*B. fasciatus*) in Myanmar. Trans R Soc Trop Med Hyg. 1997;91(6):686-8.
147. Catterall WA, Cestele S, Yarov-Yarovoy V, Yu FH, Konoki K, Scheuer T. Voltage-gated ion channels and gating modifier toxins. Toxicon. 2007;49(2):124-41.
148. Stevens M, Peigneur S, Tytgat J. Neurotoxins and their binding areas on voltage-gated sodium channels. Front Pharmacol. 2011;2:71.
149. Sato S, Kodama M, Ogata T, Saitanu K, Furuya M, Hirayama K, Kakinuma K. Saxitoxin as a toxic principle of a freshwater puffer, *Tetraodon fangi*, in Thailand. Toxicon. 1997;35(1):137-40.
150. Lebbe EK, Peigneur S, Wijesekara I, Tytgat J. Conotoxins targeting nicotinic acetylcholine receptors: an overview. Mar Drugs. 2014;12(5):2970-3004.
151. Kanchanapongkul J. Puffer fish poisoning: clinical features and management experience in 25 cases. J Med Assoc Thai. 2001;84(3):385-9.
152. Kanchanapongkul J. Tetrodotoxin poisoning following ingestion of the toxic eggs of the horseshoe crab *Carcinoscorpius rotundicauda*, a case series from 1994 through 2006. Southeast Asian J Trop Med Public Health. 2008;39(2):303-6.
153. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat Rev Dis Primers. 2017;3(1):1-21.
154. Karlson-Stiber C, Salmonson H, Persson H. A nationwide study of *Vipera berus* bites during one year-epidemiology and morbidity of 231 cases. Clin Toxicol (Phila). 2006;44(1):25-30.
155. Henderson A, Baldwin LN, May C. Fatal brown snake (Non cardiogenic pulmonary edema in a case of viperidine snake bite) envenomation despite the use of antivenom. Med J Aust. 1993;158(10):709-10.
156. Agarwal R, Singh AP, Aggarwal AN. Pulmonary oedema complicating snake bite due to *Bungarus caeruleus*. Singapore Med J. 2007;48(8):e227-30.
157. Pillai LV, Ambike D, Husainy S, Khaire A, Captain A, Kuch U. Severe Neurotoxic Envenoming and Cardiac Complications after the Bite of a 'Sind Krait' (*Bungarus cf. sindanus*) in Maharashtra, India. Trop Med Health. 2012;40(3):103-8.
158. Barbosa CM, Medeiros MS, Riani Costa CCM, Camplesi AC, Sakate M. Toad poisoning in three dogs: case reports. J Venom Anim Toxins incl Trop Dis. 2009;15(4). doi: 10.1590/S1678-91992009000400016.
159. Bengtson K, Nichols MM, Schnadig V, Ellis MD. Sudden death in a child following jellyfish envenomation by *Chiropsalmus quadrumanus*. Case report and autopsy findings. JAMA. 1991;266(10):1404-6.
160. Bompelli N, Reddy CR, Deshpande A. Scorpion bite-induced unilateral pulmonary oedema. BMJ Case Rep. 2018;2018.
161. Razi E, Malekanrad E. Asymmetric pulmonary edema after scorpion sting: a case report. Rev Inst Med Trop Sao Paulo. 2008;50(6):347-50.
162. Lehmann DF, Hardy JC. Stonefish envenomation. N Engl J Med. 1993;329(7):510-1.
163. Nagai H, Takuwa-Kuroda K, Nakao M, Oshiro N, Iwanaga S, Nakajima T. A novel protein toxin from the deadly box jellyfish (Sea Wasp, Habu-kurage) *Chiropsalmus quadrigatus*. Biosci Biotechnol Biochem. 2002;66(1):97-102.
164. Tibballs J. Australian venomous jellyfish, envenomation syndromes, toxins and therapy. Toxicon. 2006;48(7):830-59.
165. Wang ZL, Zhang SY, Hao SL, Yang WX. Neurotoxins and pore forming toxins in sea anemones: Potential candidates for new drug development. Histol Histopathol. 2022:18500.