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Review

Lonomia obliqua Envenomation: An Integrated View of Venom Biology, Systemic Pathophysiology and Translational Perspectives

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Abstract

Envenomation caused by the caterpillar *Lonomia obliqua* represents one of the most severe forms of lepidopterism, characterized by a complex systemic syndrome that involves consumptive coagulopathy, endothelial dysfunction, inflammation, and acute kidney injury. Although the biochemical properties of *Lonomia* venom have been extensively investigated, the mechanisms responsible for disease progression are often discussed separately. This review provides an updated synthesis of the biology of *L. obliqua*, the composition of its venom, and the molecular pathways associated with hemostatic imbalance, vascular injury, inflammatory activation, and renal damage. Attention is given to the biological activities of Lopap and Losac, two venom-derived proteins whose functions extend beyond coagulation and include effects on cell survival and tissue repair. By integrating evidence from toxinology, vascular biology, immunology, and nephrology, this review proposes a unified pathophysiological framework that links venom components to the systemic manifestations of lonomism. Finally, this review provides an integrated overview of *L. obliqua* envenomation, bridging venom biology, pathophysiology, and therapeutic advances while highlighting the translational potential of venom-derived molecules for future biomedical applications.

Keywords: *Lonomia obliqua*; lonomism; serine proteases; acute kidney injury; vascular endothelium; translational medicine

Key Contribution: This review integrates toxinology, vascular biology, immunology, and nephrology to establish a unified pathophysiological framework for *Lonomia obliqua* envenomation, while highlighting the pleiotropic functions and translational potential of key venom proteins such as Lopap and Losac.

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1. Introduction

Accidents involving urticating caterpillars of the genus *Lonomia* represent one of the most clinically significant forms of lepidopterism described to date and constitute an important public health concern in South America, particularly in Brazil. Unlike the predominantly local inflammatory reactions associated with most caterpillar species, *L. obliqua* envenomation causes a complex systemic syndrome characterized by severe disturbances of hemostasis, which may progress to spontaneous bleeding, consumptive coagulopathy,

endothelial dysfunction, and acute kidney injury (AKI). In severe cases, delayed diagnosis and inadequate management may result in life-threatening hemorrhage and severe organ dysfunction [1–3].

Research conducted at the Instituto Butantan has been fundamental in elucidating the molecular basis of *L. obliqua* envenomation and in developing the antilonomic serum, which remains the only specific antivenom therapy currently available [4]. These investigations have also led to the identification of biologically active venom components with unique biochemical properties, considerably expanding the understanding of coagulation regulation, fibrinolysis, vascular biology, and inflammatory signaling. Beyond their toxicological relevance, several venom-derived molecules have emerged as valuable experimental tools for investigating physiological pathways and as potential candidates for future biotechnological applications [1,2].

The geographical distribution of *L. obliqua* is mainly concentrated in the south and southeast of Brazil (especially in the states of Rio Grande do Sul, Santa Catarina, Paraná, São Paulo, Rio de Janeiro, and Minas Gerais), with reports also coming from nearby areas in Uruguay, Paraguay, and northeastern Argentina. Most cases of people coming into contact with this species have historically been reported in these regions [2,5,6]. Ecological studies indicate that this species has adapted successfully to anthropized environments, frequently inhabiting cultivated trees, orchards, and peri-urban areas, thereby increasing the probability of human exposure. Changes in land use, fragmentation of native forests, and the expansion of agricultural landscapes have likely contributed to the establishment of suitable habitats for the species, partially explaining the increasing frequency of reported accidents in recent decades [5,7].

The risk of envenomation is closely associated with the larval stage. *L. obliqua* undergoes complete metamorphosis, and its gregarious larvae remain aggregated on tree trunks during the day, where their cryptic coloration makes them difficult to detect. Human accidents occur predominantly after inadvertent contact with these urticating bristles, particularly during the later larval instars when the venom apparatus reaches its highest degree of development (Figure 1) [8]. Consequently, most accidents occur during warmer months, coinciding with periods of increased larval abundance and activity [5,7,9].

To reduce the risks of poisoning associated with *L. obliqua*, it is essential to implement safe handling and hygienic disposal protocols. Because of the high toxicity of the larvae's stinging hairs, direct hand contact should be strictly avoided. In clinical, sanitary, and agricultural control settings, recommended public health guidelines advise chemical or thermal neutralization methods, such as the targeted application of approved insecticides or immersion in hot water, to ensure the complete inactivation of the larvae before final disposal. The collected colonies are then sealed, labeled as hazardous biological material, and incinerated or disposed of in designated landfills according to local environmental health regulations to prevent secondary accidents [10].

The clinical manifestations of lonomism result from the coordinated action of multiple venom components that interfere simultaneously with several physiological systems. Experimental and clinical studies have demonstrated that *L. obliqua* venom contains procoagulant, anticoagulant, fibrinolytic, inflammatory, and vasoactive molecules capable of disrupting normal hemostatic regulation. Among the best-characterized components are Lopap (*L. obliqua* prothrombin activator protease) and Losac (*L. obliqua* Stuart–Prower factor activator), which promote the activation of prothrombin and factor X, respectively, leading to extensive consumption of coagulation factors and contributing to the hemorrhagic syndrome characteristic of severe envenomation [11–13].

Although considerable progress has been made in characterizing individual venom components and their biological activities, current knowledge remains fragmented across

studies addressing coagulation abnormalities, endothelial dysfunction, inflammatory responses, renal injury, or the biological properties of isolated toxins. Consequently, the pathophysiology of lonomism is often interpreted through individual mechanisms rather than as a dynamic process involving continuous interactions among vascular, inflammatory, immunological, and hemostatic pathways.

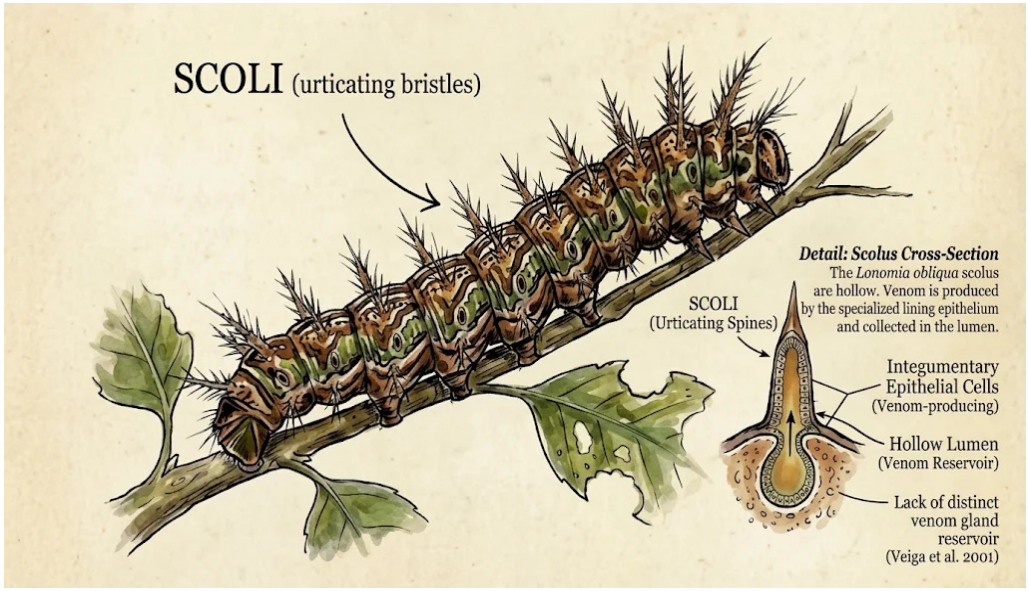


Figure 1. Artistic and schematic representation of *Lonomia obliqua* larva. General view of the caterpillar on a branch, highlighting the urticating structures (scoli) and a detailed schematic cross-section of the venom apparatus based on [8]. Note the absence of a distinct bulbous venom gland reservoir; venom is produced by the specialized integumentary epithelial cells lining the hollow lumen of each scolus. Note: This is a conceptual artistic illustration created using digital generative tools for workflow visualization purposes.

This review provides an integrated analysis of *L. obliqua* venom biology and the molecular mechanisms driving human envenomation. By combining perspectives from toxinology, vascular biology, immunology, and nephrology, we examine how consumptive coagulopathy, endothelial activation, systemic inflammation, and acute kidney injury act synergistically in severe lonomism. Additionally, we evaluate the biotechnological potential of key venom components, focusing on Lopap and Losac, and highlight current knowledge gaps to guide future research in the field.

2. Results and Discussion

2.1. Venom Composition and Major Bioactive Molecules

The venom of *L. obliqua* is a complex mixture of biologically active molecules that interact dynamically with multiple physiological systems. Unlike venoms dominated by a single major toxin family, the clinical manifestations of lonomism result from the synergistic activity of several components with distinct biochemical properties, concurrently affecting coagulation, fibrinolysis, vascular homeostasis, inflammatory responses, and cellular signaling pathways. This molecular diversity underlies the complexity of the clinical syndrome and explains the broad spectrum of systemic alterations observed after envenomation [1,2].

Among the proteolytic components characterized in *Lonomia* venoms, enzymes displaying serine protease-like activity represent a prominent group due to their ability to selectively cleave proteins of the coagulation cascade [14,15]. However, unlike classical

vertebrate serine proteases that rely on a canonical catalytic triad (Ser-His-Asp) within a chymotrypsin-like fold, the major hemostatically active proteins isolated from *L. obliqua* belong to atypical molecular families [12,16,17]. Specifically, Lopap (*L. obliqua* prothrombin activator protease) is a 69 kDa native homodimeric complex (composed of ~22.5 kDa monomers) structurally classified within the lipocalin family yet exhibiting serine protease-like catalytic activity [10,18]. Similarly, Losac (*L. obliqua* Stuart–Prower factor activator) is a 43–45 kDa protein belonging to the hemolin family, an insect-specific member of the immunoglobulin superfamily that directly cleaves and activates Factor X without sharing canonical serine protease sequence homology [11,17,19].

Other enzymatic families commonly found in animal venoms, such as phospholipases and matrix metalloproteinases (MMPs), are involved in membrane hydrolysis, lipid mediator generation, and extracellular matrix remodeling [20–22]. In *L. obliqua*, a calcium-dependent phospholipase A_2 (PLA_2) has been purified and biochemically characterized from bristle extracts, demonstrating indirect hemolytic activity and a potential contribution to membrane destabilization and inflammatory signaling [23]. Conversely, while gelatinolytic and metalloproteinase-like activities have been detected in crude extracts, the structural identity and relative quantitative contribution of MMPs in *L. obliqua* venom remain incompletely mapped [16,19].

Despite substantial advances over the past two decades, the complete molecular landscape of *L. obliqua* venom has not yet been fully mapped. Several protein fractions remain only partially characterized, and the precise functional interactions among individual venom components are still poorly understood. Future studies integrating high-throughput proteomics, structural biology, and functional assays will be essential to determine how these molecules act in concert to produce the systemic manifestations of envenomation. The principal venom components characterized to date, together with their molecular targets and biological activities, are summarized in Table 1.

Table 1. Major molecular components associated with *Lonomia* envenomation and their biological effects, with emphasis on characterized toxins from *L. obliqua*.

Category	Component	Molecular Target/Activity	Biological Effects Described in Envenomation	References
Procoagulant lipocalin (with serine protease-like activity)	Lopap (*L. obliqua* prothrombin activator protease)	Direct activation of prothrombin (independent of the prothrombinase complex) with thrombin generation	Contribution to procoagulant activity, endothelial activation, and consumption of coagulation factors observed in *L. obliqua* envenomation	[2,12,18]
Procoagulant hemolin (immunoglobulin superfamily)	Losac (*L. obliqua* Stuart–Prower factor activator)	Direct cleavage and activation of Factor X into Factor Xa	Participation in coagulation activation, fibrinolytic modulation, and hemostatic imbalance during *L. obliqua* envenomation	[11,17,19]
Fibrinolytic/Proteolytic enzymes	Lonomins (primarily characterized in *L. achelous*)	Direct proteolytic/fibrinogenolytic activity against fibrinogen, fibrin, and coagulation-related substrates	Alteration of coagulation pathways and contribution to hemorrhagic manifestations described primarily for *L. achelous* envenomation	[1,19]

2.2. Molecular Basis of Hemostatic Dysregulation

The defining feature of *L. obliqua* envenomation is a profound disruption of hemostatic homeostasis. Rather than acting exclusively as either a procoagulant or anticoagulant agent, the venom simultaneously activates clotting pathways while disrupting the regulatory mechanisms responsible for maintaining vascular integrity. This complex imbalance culminates in consumptive coagulopathy, a hallmark of severe lonomism that predisposes patients to spontaneous bleeding despite the widespread activation of the coagulation cascade [1,19,24].

This process is driven primarily by the coordinated action of Lopap and Losac. Lopap directly cleaves prothrombin through a mechanism distinct from the physiological prothrombinase complex, resulting in rapid thrombin generation, whereas Losac activates factor X, further amplifying upstream coagulation signaling [17,18]. Although these specialized reactions initially promote fibrin formation, their sustained and unregulated activation accelerates the consumption of clotting factors, progressively exhausting the hemostatic reserve required for effective vascular repair [24].

Clinical observations closely mirror these experimental findings. Patients with severe envenomation characteristically exhibit prolonged clotting times, marked hypofibrinogenemia, reduced circulating levels of multiple coagulation factors, and increased concentrations of fibrin/fibrinogen degradation products (FDPs), reflecting intense activation followed by a sharp depletion of clotting factors [25]. These laboratory abnormalities parallel the progression of clinical manifestations, including persistent bleeding from venipuncture sites, mucosal hemorrhage, ecchymoses, hematomas, hematuria, and, in severe cases, life-threatening internal or intracranial bleeding [26].

2.3. Endothelial Alterations and Inflammatory Amplification

The vascular endothelium is a primary target of *L. obliqua* venom and appears to contribute substantially to the progression from a localized venom exposure to systemic disease. In addition to functioning as a selective barrier, endothelial cells actively participate in regulating coagulation, vascular permeability, leukocyte trafficking, and inflammatory responses. Therefore, endothelial activation represents a critical mechanistic link between venom-induced hemostatic disturbances and the macro- and microvascular abnormalities observed in severe lonomism [1,19].

Experimental studies indicate that *L. obliqua* venom components disrupt multiple cellular targets through distinct molecular pathways [16]. Purified molecules, particularly Lopap and Losac, as well as whole venom extracts, alter endothelial activation, oxidative stress responses, cell migration, extracellular matrix interactions, and inflammatory signaling. The primary cellular targets and biological effects characterized to date are synthesized in Table 2.

Exposure of endothelial cells to Lopap increases the expression of key cell adhesion molecules, including E-selectin and intercellular adhesion molecule-1 (ICAM-1), indicating a transition toward an activated endothelial state. This up-regulation suggests a potential role for Lopap in modulating early interactions between the vascular wall and circulating leukocytes [1,27]. Consequently, the biological footprint of Lopap extends far beyond direct thrombin generation, encompassing the active modulation of endothelial pro-inflammatory signaling pathways [27].

Losac displays a distinct yet complementary functional profile. In addition to activating factor X and driving downstream coagulation cascades, Losac stimulates endothelial nitric oxide (NO) production and promotes the release of tissue plasminogen activator (t-PA) [17]. These concomitant effects suggest that Losac acts as a modulator of endothe-

lial signaling and fibrinolytic regulation, further exacerbating the homeostatic imbalance between procoagulant forces, vascular tone, and fibrinolytic control during envenomation.

Table 2. Cellular targets, molecular pathways, and functional outcomes modulated by *Lonomia obliqua* venom components and extracts.

Target Cell Type	Venom Component/Extract	Molecular Pathways Involved	Functional/Biological Outcome	Key References
Endothelial Cells	Lopap	Up-regulation of E-selectin and ICAM-1	Endothelial activation; modulation of leukocyte–endothelial interactions	[1,27]
Endothelial Cells	Losac	Stimulates Nitric Oxide (NO) production and t-PA release	Modulation of vascular tone, cell signaling, and fibrinolytic regulation	[17]
Vascular Smooth Muscle Cells (VSMCs)	LOCBE (Bristle Extract)	NADPH oxidase activation, ROS production, ERK signaling	Cytoskeletal rearrangements, increased cell migration and proliferation	[28]
Vascular Cells	Bristle Extract	Rac1-dependent signaling; FAK phosphorylation	Disruption of focal adhesions, altered paxillin and vinculin distribution	[29]
Endometrial Stromal Cells	Non-hemotoxic fractions	NO, PKC/ERK, and cAMP/PKA pathways	Cellular survival, proliferation, and protection against oxidative stress	[30]
Macrophages (THP-1)	Whole Venom	NF-κB activation	Release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, CXCL10)	[3]

Note: cAMP, cyclic adenosine monophosphate; CXCL10, C-X-C motif chemokine ligand 10; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; LOBE, *L. obliqua* bristle extract; LOCBE, *L. obliqua* caterpillar bristle extract; Lopap, *L. obliqua* prothrombin activator protease; Losac, *L. obliqua* Stuart–Prower factor activator (factor X activator); NO, nitric oxide; NF-κB, nuclear factor kappa B; PKA, protein kinase A; PKC, protein kinase C; ROS, reactive oxygen species; t-PA, tissue plasminogen activator; TNF-α, tumor necrosis factor alpha.

The pathological effects of *L. obliqua* venom are not restricted to the endothelium. Investigations using vascular smooth muscle cells (VSMCs) have demonstrated that venom-derived extracts stimulate intracellular networks associated with oxidative stress, migration, and proliferation. Moraes et al. [28] demonstrated that *L. obliqua* caterpillar bristle extract (LOCBE) induces robust reactive oxygen species (ROS) production via NADPH oxidase activation, followed by downstream mitochondrial oxidative signaling. This cascade triggers extracellular signal-regulated kinase (ERK) activation, cytoskeletal rearrangements, and increased VSMC migration and proliferation, indicating that venom components may also influence vascular remodeling.

Concurrently, alterations in cell migration and adhesion have been characterized by Bernardi et al. [29], who showed that *L. obliqua* bristle extract modifies Rac1-dependent signaling pathways involved in cytoskeletal organization. Proteomic and functional analyses revealed structural remodeling of focal adhesions and altered distribution of adhesion-associated proteins, including paxillin and vinculin, alongside increased focal adhesion kinase (FAK) phosphorylation. These findings indicate that venom-derived molecules can interfere with highly conserved mechanisms governing cell–matrix interactions.

Although most investigations emphasize the deleterious pathways associated with acute envenomation, recent evidence indicates that specific venom-derived fractions can induce contrasting cellular responses depending on the experimental microenvironment. de Almeida Schneider et al. [30] reported that non-hemotoxic fractions obtained from *L. obliqua* venom secretions promoted the survival, proliferation, and migration of human endometrial stromal cells while mitigating oxidative stress-induced injury. Quantitative proteomics identified candidate molecules, including lipocalin-related proteins and protease

inhibitors, linked to these cytoprotective responses. The observed phenotypes involved the activation of NO- and PKC/ERK-dependent pathways, alongside the modulation of cAMP/PKA signaling, reinforcing the molecular complexity of *L. obliqua* secretomes.

In addition to its vascular effects, *L. obliqua* venom triggers innate immune pathways that amplify systemic inflammation. Oliveira et al. [3] demonstrated that venom exposure induces nuclear factor-kappa B (NF-κB) activation in THP-1-derived macrophages, stimulating the secretion of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, and CXCL10. These results provide experimental backing for the active involvement of immune cells in the inflammatory cascade of lonomism.

Taken together, current evidence suggests that endothelial dysfunction, oxidative stress, and inflammation are deeply interconnected processes during *L. obliqua* envenomation. Endothelial activation increases vascular permeability and impairs microcirculatory homeostasis, worsening the consequences of consumptive coagulopathy. Simultaneously, circulating inflammatory mediators sustain leukocyte activation and oxidative tissue injury. Available data support a robust, multifactorial pathophysiological model in which hemostatic dysregulation, vascular activation, and inflammatory responses develop concurrently rather than via a single, isolated toxic mechanism [3,19].

The rapid onset of systemic manifestations observed in clinical settings reflects the efficiency of these overlapping biological cascades. Peruzzo and Gössling [31] documented a patient who developed hematuria and extensive spontaneous ecchymoses within hours of accidental contact with *L. obliqua*, illustrating the aggressive tempo of the hemorrhagic syndrome. These observations underscore the critical importance of early diagnosis and specific antilonomic serotherapy before secondary complications, such as inflammatory amplification and multi-organ damage, become irreversibly established.

2.4. Acute Kidney Injury: A Multifactorial Consequence of Hemodynamic, Microvascular, and Inflammatory Injury

Acute kidney injury (AKI) is among the most clinically critical complications associated with severe *L. obliqua* envenomation and is frequently linked to unfavorable clinical outcomes. Renal damage in lonomism does not appear to result from the isolation of a single, highly specific nephrotoxic molecule. Instead, it arises from the synergistic convergence of systemic hemodynamic disturbances, endothelial injury, consumptive coagulopathy, acute inflammatory activation, oxidative stress, and direct tubular damage. The dynamic interplay among these pathological processes drives the rapid deterioration of renal function frequently documented in severe clinical presentations [3,26].

Early renal dysfunction is closely tied to alterations in effective circulating intravascular volume. Severe hemorrhage triggered by venom-induced coagulation abnormalities, coupled with accelerated vascular permeability from endothelial activation, can dramatically reduce renal blood flow and compromise the glomerular filtration rate (GFR). This profound hypoperfusion establishes an ischemic microenvironment for tubular cells, markedly amplifying their susceptibility to concomitant toxic insults. Experimental studies have confirmed that *L. obliqua* venom disrupts vascular regulation via inflammatory and vasoactive pathways, including the robust activation of the kallikrein–kinin system, which actively promotes hemodynamic instability and microvascular leakage [26,32,33].

As the systemic manifestations of envenomation mature, severe disturbances in hemostasis further compromise the renal microcirculation. The unmitigated activation of coagulation pathways, followed by the exhaustion of clotting factors, is accompanied by structural vascular changes that restrict local perfusion within the renal parenchyma. Histopathological analyses of experimental *L. obliqua* envenomation have identified prominent endothelial swelling, intravascular fibrin deposition, and structural abnormalities

compatible with microvascular injury, confirming that localized microcirculatory impairment is a core driver of AKI development [26,32].

Renal injury may also be exacerbated by pigment-mediated oxidative damage. In severe envenomation, extensive bleeding and intravascular hemolysis can expose renal tubules to cell-free hemoglobin and heme. While free heme is a well-established driver of iron-dependent reactive oxygen species (ROS) generation, lipid peroxidation, and tubular toxicity in systemic hemolytic conditions [34,35], direct clinical evidence of pigment nephropathy in human lonomism has recently been corroborated by renal biopsy findings demonstrating acute tubular injury accompanied by intratubular pigmented casts [36].

Inflammation represents another pivotal vector of renal injury. Beyond its established effects on coagulation and vascular tone, *L. obliqua* venom triggers innate immune networks that amplify systemic inflammation. Experimental models have demonstrated the activation of nuclear factor-kappa B (NF-κB) signaling and a robust up-regulation of cytokines and chemokines by venom-exposed macrophages, supporting the view that immune activation is central to systemic toxicity [3]. Within the renal parenchyma, sustained pro-inflammatory signaling promotes leukocyte recruitment, fuels oxidative stress, and accelerates progressive tubular dysfunction.

Evidence from both experimental models and human pathology indicates that renal involvement in lonomism affects multiple anatomical compartments. In rodent models, Berger et al. [26] documented widespread tubular degeneration, glomerular fibrin deposition, endothelial swelling, and interstitial inflammatory infiltration, while pharmacological kallikrein inhibition attenuated these renal alterations, underscoring the role of kinin-mediated hemodynamic and vascular injury [33]. Complementing these preclinical observations, histopathological analysis of a kidney biopsy from a patient with severe *L. obliqua* envenomation confirmed acute tubular necrosis, pigmented casts, and microvascular injury compatible with thrombotic microangiopathy [36].

From a clinical perspective, acute kidney injury remains the primary cause of mortality in severe *L. obliqua* envenomation [37]. Randomized clinical trial data have demonstrated that specific antilonomic serum is highly effective in reversing venom-induced consumptive coagulopathy and restoring fibrinogen levels [4]. However, robust clinical evidence directly establishing the optimal therapeutic time window to prevent AKI or reduce the need for renal replacement therapy remains limited. Historical cohorts including patients managed prior to the routine availability of antilonomic serum indicate that prolonged, untreated coagulopathy and delayed hospital admission are associated with severe renal outcomes [37,38]. Thus, while early serotherapy is strongly recommended on pathophysiological grounds to halt ongoing thrombin generation and microvascular fibrin deposition before irreversible parenchymal damage occurs, dedicated prospective clinical studies are still needed to define the precise impact of treatment timing on renal endpoints [4,38].

Consequently, AKI associated with *L. obliqua* envenomation must be conceptualized as the cumulative result of successive and overlapping insults rather than an isolated pathogenic event. Initial drops in renal perfusion occur concurrently with endothelial dysfunction, coagulation-related microvascular injury, oxidative stress, and active inflammatory cascades. These interconnected mechanisms develop in parallel and reinforce one another during disease progression, worsening the severity of AKI. The primary mechanisms implicated in renal dysfunction during severe lonomism are categorized and summarized in Figure 2 and Table 3.

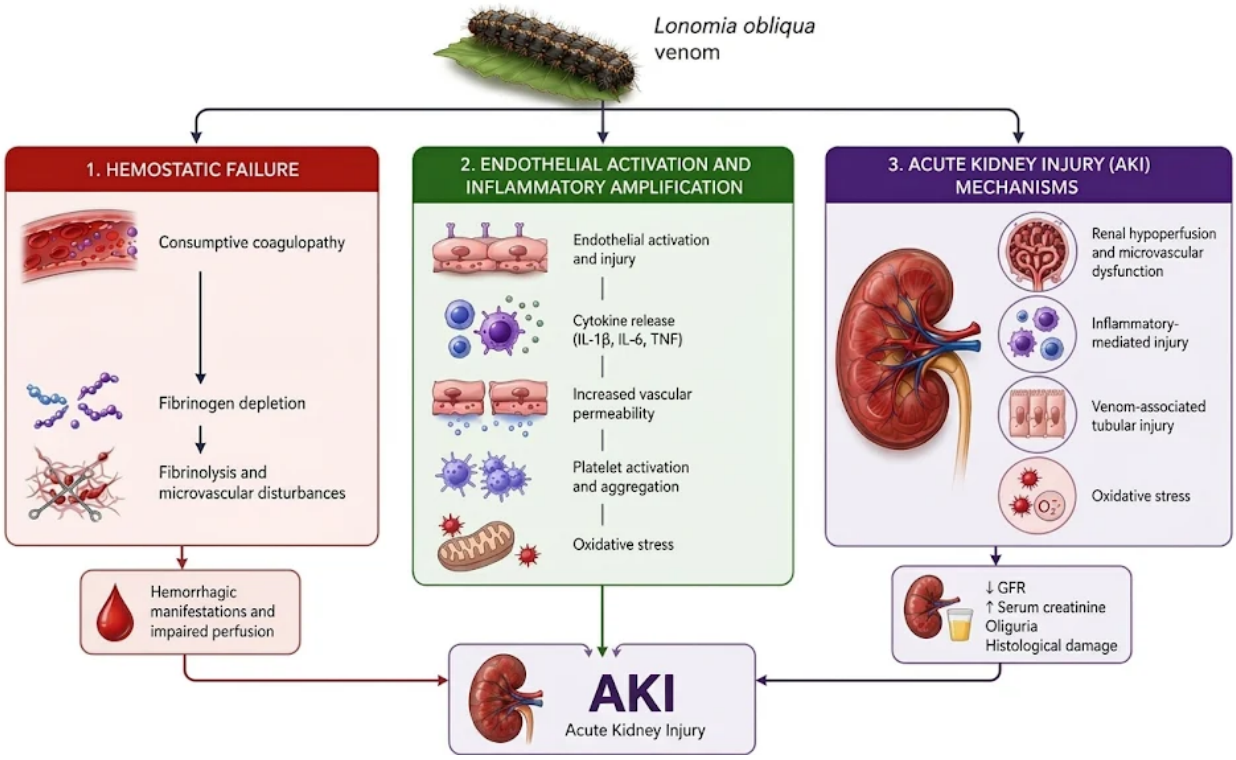


Figure 2. Integrated pathophysiological mechanisms leading to AKI in severe *L. obliqua* envenomation. Severe lonomism induces a multifactorial pathogenic cascade involving three interconnected processes: hemostatic failure, endothelial activation with inflammatory amplification, and acute kidney injury. Venom-induced consumptive coagulopathy, fibrinogen depletion, fibrinolytic activity, and microvascular disturbances promote hemorrhagic manifestations and impair tissue perfusion. Concurrent endothelial activation triggers inflammatory cytokine release (IL-1β, IL-6, and TNF), endothelial injury, increased vascular permeability, platelet activation, and oxidative stress. Together, these systemic alterations culminate in renal hypoperfusion, microvascular dysfunction, inflammatory-mediated injury, and venom-associated tubular injury, ultimately leading to AKI. The figure illustrates how coagulation abnormalities, endothelial dysfunction, and inflammation act synergistically to drive renal injury during severe lonomism. Upward arrows (↑) indicate increase, and downward arrows (↓) indicate decrease. Note: This illustration was conceptualized by the authors and generated with the assistance of artificial intelligence (AI) tools, followed by human curation and rigorous scientific verification for conceptual and anatomical accuracy.

Table 3. Pathophysiological classification and mechanisms contributing to acute kidney injury (AKI) in *L. obliqua* envenomation.

Injury Category	Pathophysiological Basis	Primary Renal and Histopathological Findings
Prerenal (Hemodynamic)	Effective intravascular volume depletion driven by severe hemorrhage, vascular leakage, and kallikrein–kinin system activation [19,32,33].	Renal hypoperfusion and an acute functional reduction in glomerular filtration rate (GFR) prior to established parenchymal necrosis (Clinical: hemodynamic instability in severe bleeding [34,35]; Experimental: hypotension and kinin-mediated leakage in rat models [26,32,33]).
Intrinsic-Tubular (Ischemic & Direct)	Sustained hypoperfusion-induced ischemia, reactive oxygen species (ROS) oxidative stress, NF-κB-driven interstitial inflammation, and direct venom toxicity [3,26].	Acute tubular necrosis (ATN), tubular epithelial cell degeneration/apoptosis, and interstitial inflammatory infiltration (Clinical: human renal biopsy [36]; Experimental: rodent histopathology [26]).

Table 3. *Cont.*

Injury Category	Pathophysiological Basis	Primary Renal and Histopathological Findings
Intrinsic-Tubular/(Pigment-related)	Tubular epithelial injury and luminal obstruction associated with cell-free hemoglobin/heme release following severe bleeding or intravascular hemolysis [34,35].	Intratubular pigment casts, tubular obstruction, and heme-driven oxidative tubular injury (Clinical: pigment casts documented in human renal biopsy [36]; Mechanistic extrapolation: heme nephrotoxicity pathways [34,35]).
Intrinsic-Microvascular	Endothelial activation/injury, consumptive coagulopathy, and localized intravascular fibrin deposition [26,32].	Endothelial swelling, glomerular capillary microthrombi, impaired cortical perfusion, and thrombotic microangiopathy (TMA)-like features (Clinical: TMA-like microvascular injury in human biopsy [36]; Experimental: glomerular fibrin deposition and endothelial swelling in rats [26,32]).

Note: AKI, acute kidney injury; GFR, glomerular filtration rate; ROS, reactive oxygen species, TMA, Thrombotic Microangiopathy.

3. Translational Perspectives and Biotechnological Tools

3.1. Beyond Toxicity: The Functional Duality of Lopap and Losac

Research on *L. obliqua* venom has historically focused on deciphering the molecular mechanisms responsible for the severe hemorrhagic syndrome associated with lonomism. However, the systematic characterization of individual venom components has revealed that several of these molecules possess biological activities extending far beyond their contribution to acute systemic toxicity. Among them, Lopap and Losac have garnered significant attention because, in addition to their well-established procoagulant phenotypes, they can actively modulate evolutionarily conserved cellular pathways involved in survival, inflammation, and tissue responses.

Lopap represents a premier archetype of this biological duality. Initially characterized as a prothrombin activator driving systemic consumptive coagulopathy, Lopap was subsequently shown to trigger cellular signaling independent of its direct proteolytic role within the coagulation cascade [17,27]. This dual functional repertoire underscores the complexity of venom-derived scaffolds, whose biological downstream effects can vary dramatically depending on concentration, cellular microenvironment, and specific experimental designs.

In vitro assays utilizing recombinant Lopap (rLopap) have demonstrated that, under controlled experimental conditions, the protein promotes the survival of both endothelial cells and neutrophils by mitigating apoptosis induced by serum deprivation. These cytoprotective effects appear to depend, at least partially, on endothelial NO production, given that the pharmacological inhibition of NO synthases significantly blunts the rLopap-mediated survival response. Crucially, rLopap did not trigger deleterious leukocyte–endothelial interactions in vivo within the evaluated models, suggesting that its cytoprotective signaling pathways are not obligatorily coupled to overt pro-inflammatory activation [39].

The biological effects of Lopap (a lipocalin displaying serine protease-like activity) and Losac have also been explored across non-vascular cell lineages. Recent investigations have demonstrated that both recombinant Lopap (rLopap) and recombinant Losac (rLosac) influence skeletal muscle precursor cells, stimulating myoblast proliferation and modulating key myogenic regulatory factors through mechanisms dependent on prostaglandin PGE2 release and downstream activation of the EP4 receptor [40]. While these findings do not yet establish an immediate regenerative application for wild-type Lopap, they considerably expand the known biological boundaries of this protein and indicate that its non-catalytic signaling properties may yield valuable mechanistic insights into tissue repair and cellular remodeling networks.

Losac offers a parallel example of functional diversity among *L. obliqua* venom constituents. Initially isolated as factor X activator involved in catastrophic hemostatic dysregulation, Losac was later shown to modulate endothelial cell physiology, driving NO production and stimulating tissue plasminogen activator (t-PA) release [17]. These lines of evidence indicate that Losac targets regulatory pathways governing vascular patency, supporting the paradigm that venom-derived proteins harbor structurally distinct domains capable of modulating physiological processes independently of their toxic catalytic activities.

The discovery of regulatory and cytoprotective motifs within venom components has broadened the scope of modern toxinology, shifting the discipline from the classic characterization of harmful molecules toward the exploration of bio-inspired proteins as robust research tools. Characterized venom molecules have contributed significantly to mapping complex physiological networks, including coagulation kinetics, inflammatory cascades, cell migration, and extracellular matrix turnover. In this framework, Lopap and Losac represent elegant molecular models for examining how extracellular proteins can simultaneously coordinate enzymatic substrate cleavage and intracellular receptor signaling.

3.2. Engineered Recombinant Variants and Smart Biomaterials

Despite the biological duality of these proteins, translating wild-type *L. obliqua* toxins into safe therapeutic agents poses substantial challenges. Their endogenous biological potencies must be precisely decoupled, as the exact properties that make them attractive molecular probes can disrupt homeostatic coagulation cascades. Critical translational hurdles, including strict dose optimization, target specificity, systemic immunogenicity, protein stability, and long-term bio-safety, must be comprehensively resolved before clinical translation can be envisioned.

One promising strategy centers on the generation of engineered recombinant variants designed to preserve cytoprotective signaling domains while selectively abolishing undesirable procoagulant catalytic activities. Exploiting state-of-the-art advances in structural biology, computational protein design, and site-directed mutagenesis may streamline the synthesis of safer bio-derivatives with finely tuned therapeutic windows. Concurrently, targeted delivery vehicles and biomaterial-embedded matrices could restrict systemic exposure, maximizing the localized bio-activity of these venom-derived motifs.

Emerging biomaterial platforms, such as stimulus-responsive hydrogels and nanocarriers, offer exciting avenues for the controlled delivery of bioactive proteins within pathological niches defined by chronic inflammation, localized oxidative stress, or deregulated protease environments [41,42]. Although these integration strategies remain exploratory regarding *L. obliqua* toxins, they highlight how mechanistic insights harvested from toxinology can merge with advanced drug delivery to seed future biomedical technologies.

In summary, the scientific value of Lopap and Losac extends well beyond their classic roles in the pathophysiology of lonomism. These proteins stand as compelling examples of how venom components can be repurposed as biological keys to unlock cellular regulation, offering structural baselines for future molecular engineering endeavors [43]. Continued interdisciplinary research combining high-resolution structural biology, recombinant expression technologies, and sophisticated primary cell cultures will be mandatory to determine whether these venom-derived dynamics can be safely harnessed for future regenerative medicine and pharmacological discovery.

3.3. Knowledge Gaps and Future Perspectives

Despite major advances in characterizing *L. obliqua* venom and the molecular networks driving lonomism, several fundamental questions remain unanswered. Research over the last few decades has progressively shifted from descriptive clinical epidemiology and basic

toxin isolation toward high-resolution molecular and cellular investigations. However, the precise way distinct venom components interact with one another and with host physiological cascades to dictate disease progression or facilitate tissue recovery remains only partially mapped. Resolving these mechanistic enigmas is vital not only for refining clinical management but also for evaluating whether venom-derived scaffolds can be safely repurposed as biotherapeutic tools.

High-throughput proteomic and transcriptomic surveys of *L. obliqua* bristles and teguments have identified numerous supplementary protein families with putative biological activities; however, many of these transcripts and proteins remain poorly defined regarding their exact molecular targets, cellular effects, and synergistic contribution to the clinical presentation of envenomation [2,44].

An equally compelling challenge lies in deciphering how an initially localized caterpillar exposure rapidly transitions into a disastrous systemic disorder involving concurrent consumptive coagulopathy, macrovascular dysfunction, profound inflammation, and multi-organ damage. Although these microenvironments have been individually studied, their precise temporal relationships, feedback loops, and relative hierarchy during clinical progression remain elusive. Pinpointing the earliest molecular and biochemical events triggered immediately after venom injection may help differentiate the primary drivers of tissue pathology from secondary, host-mediated cascades that amplify organ injury [45].

The crosstalk between *L. obliqua* venom components and the host innate immune system represents another frontier requiring rigorous exploration. Experimental models have documented the robust activation of nuclear factor-kappa B (NF-κB) signaling and a subsequent spike in pro-inflammatory mediators following venom exposure [3]; however, the spatial recruitment and functional contribution of specific immune cell populations during distinct evolutionary stages of envenomation remain largely unknown. Methodologies integrating deep immune profiling, single-cell RNA sequencing (scRNA-seq), and spatial transcriptomics could provide a high-resolution understanding of how localized and systemic immune responses dictate vascular injury, drive renal dysfunction, or influence tissue recovery following specific antilonomic serotherapy.

Renal complications also persist as a critical focal point for future research. While clinical and experimental studies have firmly established the overlapping involvement of hemodynamic collapses, endothelial injury, microvascular fibrin deposition, and localized inflammatory infiltrates in lonomism-associated AKI [33,37], the precise molecular switches that govern the progression toward irreversible parenchymal damage versus successful functional recovery remain poorly understood. The identification and validation of early, non-invasive clinical biomarkers of renal stress, podocyte injury, or endothelial cell activation could dramatically improve risk stratification and support more individualized, preemptive clinical protocols.

From a translational perspective, one of the premier bottlenecks is determining whether the cytoprotective or regulatory properties observed for isolated venom components can be structurally decoupled from their lethal systemic effects. Lopap and Losac elegantly illustrate this evolutionary complexity: both proteins act as major drivers of coagulopathy during systemic envenomation, yet experimental assays have also uncovered non-catalytic properties that govern endothelial survival, myogenic signaling, and tissue repair [11,17,40]. Mapping the exact structural determinants and distinct domains responsible for these contrasting biological actions is an absolute prerequisite for any future molecular engineering endeavor.

Potential mitigation strategies include designing recombinant variants, truncated domains, or synthetic peptidomimetics engineered to retain cytoprotective signaling functions while selectively abolishing undesirable procoagulant enzyme kinetics. Rapid advances

in computational protein design, high-resolution structural biology, and targeted nano-delivery systems may accelerate this pipeline; however, these cutting-edge platforms are still in conceptual stages and demand exhaustive validation regarding target specificity, long-term stability, systemic immunogenicity, and safety profiles.

Furthermore, emerging state-of-the-art experimental platforms, including human organoid models, organ-on-a-chip microfluidic systems, and biomimetic scaffolds, could provide more physiologically faithful environments for investigating venom biology. These bio-convergent technologies have the potential to bridge the traditional chasm between descriptive toxin characterization and translational molecular engineering by allowing researchers to monitor the real-time interactions among vascular networks, circulating immune cell subsets, and target parenchymal tissues under highly controlled, human-relevant biological contexts.

Overall, current evidence supports a holistic conceptualization of *L. obliqua* venom as a complex biological system rather than a mere cocktail of harmful toxins. Its specialized constituents have already yielded invaluable insights into the intricacies of coagulation kinetics, inflammatory signaling, and cell survival regulation. The grand challenge for the next generation of researchers will be to safely translate this rich mechanistic knowledge into clinically meaningful biomedical applications while maintaining a rigorous, evidence-based distinction between theoretical biological potential and experimentally validated therapeutic utility.

4. Conclusions

L. obliqua envenomation represents a complex systemic disorder resulting from the coordinated action of multiple venom components that concurrently disrupt hemostasis, endothelial integrity, inflammatory cascades, and organ homeostasis. The overall clinical severity of lonomism reflects a dynamic, multifaceted interaction between venom-derived molecules and host physiological responses, rather than the isolated effect of a single toxic mechanism.

Significant advances in toxin characterization, particularly the molecular isolation of Lopap and Losac, have elucidated the biochemical pathways underlying envenomation. While in vivo experimental models have demonstrated how these purified toxins directly trigger intravascular coagulation cascades, alter vascular permeability, and drive endothelial activation, clinical studies in patients confirm that these cellular processes drive the consumptive coagulopathy, severe bleeding manifestations, and acute organ disruption observed in human lonomism. Furthermore, the study of these specialized proteins has expanded the traditional boundaries of venom biology beyond mere acute toxicity, revealing their immense value as molecular scaffolds for investigating intracellular signaling pathways and broader biological regulation.

By integrating in vivo experimental evidence and clinical observations across toxinology, vascular biology, immunology, and nephrology, this review highlights the deeply interconnected mechanisms driving *L. obliqua* envenomation. Ultimately, these insights reinforce the critical importance of a multidisciplinary framework, which remains essential not only for fully understanding systemic disease progression but also for shaping future translational research directions and biotherapeutic innovation.

Finally, consolidating this mechanistic understanding into improved clinical outcomes remains the primary objective for novel therapeutic strategies. Although antilonomic serotherapy remains the only specific treatment available, a multi-target therapeutic approach that addresses systemic inflammation, vascular permeability, and renal impairment alongside venom neutralization could significantly reduce the morbidity and mortality associated with *L. obliqua* envenomation. Sustained cross-disciplinary collaboration is es-

sential to bridge basic toxinology with clinical practice. This integration will ensure that emerging biological discoveries translate into more accurate diagnoses, targeted adjunct therapies, and safer, more effective management protocols for lonomism.

5. Methods

This narrative review was conducted to provide an integrated overview of current knowledge on *L. obliqua* envenomation, with particular emphasis on venom composition, molecular mechanisms, clinical manifestations, and emerging translational perspectives. The overall goal was to synthesize robust evidence from experimental, clinical, and epidemiological studies addressing the pathophysiology of lonomism.

A structured literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, and SciELO databases. Publications available in English, Portuguese, or Spanish were considered without restriction on publication date. This comprehensive approach allowed for the incorporation of both classical studies that established the foundations of the field and recent investigations addressing current advances in venom biology and translational research.

The search strategy combined relevant controlled vocabulary terms (such as MeSH and DeCS) and free-text keywords related to *Lonomia* biology and envenomation. The principal search terms included "*Lonomia*", "*Lonomia obliqua*", "envenoming", "venom", "coagulopathy", "blood coagulation disorders", "acute kidney injury", "endothelial dysfunction", "inflammation", "serine proteases", "Lopap", and "Losac", which were combined using the Boolean operators AND and OR.

The retrieved publications were assessed according to their methodological relevance and specific contribution to the objectives of this review. Original research articles, experimental studies, clinical investigations, case reports, review articles, and official reports from health authorities were considered eligible. Whenever available, priority was given to peer-reviewed original studies providing molecular and experimental evidence, whereas review articles were primarily utilized to provide historical context, summarize established concepts, and support broader scientific interpretation. Special attention was dedicated to studies addressing venom composition, toxin characterization, mechanisms of hemostatic dysregulation, endothelial and inflammatory responses, acute kidney injury, and the therapeutic efficacy of antilonomic serum. Duplicate records and publications lacking direct relevance to the biological, toxicological, molecular, or clinical aspects of *L. obliqua* envenomation were excluded.

The selected evidence was qualitatively analyzed and synthesized into thematic sections to provide an integrated interpretation of the current literature. Rather than discussing individual findings in isolation, this review combines evidence from toxinology, vascular biology, immunology, and nephrology to examine the interconnected mechanisms involved in disease progression. Crucially, areas where evidence remains limited or incomplete are highlighted to identify priorities for future experimental and translational research.

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