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A Scoping Review on Venom Toxicity of Pakistani Brown Cobra (*Naja oxiana*): Emerging Synthetic Therapeutics and Challenges in Current Treatment Approaches

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A B S T R A C T

Background: The Pakistani brown cobra (*Naja oxiana*) is a medically significant species widely distributed across Pakistan, India, Afghanistan, and Bangladesh. Its venom exhibits potent neurotoxic, cardiotoxic, and cytotoxic activities, leading to significant morbidity and mortality in rural and peri-urban populations. Despite the availability of conventional polyvalent antivenoms, limitations such as low specificity, variable efficacy, still many adverse reactions persist. Recent years have seen an increased interest in synthetic inhibitors and small-molecule compounds targeting venom enzymes, with the goal of improving treatment outcomes. **Objective:** To assess the (2015–2025) toxicity of *N. oxiana* venom, assess reported synthetic/chemical analogues that demonstrate *in vitro* or *in vivo* neutralizing activity, and evaluate shortcomings of existing polyvalent antivenoms. **Methodology:** A scoping review was conducted in accordance with JBI guidelines. Databases (PubMed, Scopus, EMBASE, Web of Science) were searched for English-language studies (2015–2025) focusing on *N. oxiana*, its venom composition, synthetic inhibitors, and antivenom performance in countries with these snakes. Data extraction captured study design, venom components, inhibitor type, mechanism of action, IC50/ED50 values, p-values were reported, and antivenom efficacy. **Results:** We selected 70 records out of which 15 met our inclusion criteria. Venom proteomics consistently report high abundances of phospholipase A_2 (PLA_2), Alkaline Phosphatases (ALP), three-finger toxins (3FTx), snake venom metalloproteinases (SVMPs), hyaluronidase, and L-amino acid oxidase (LAAO). Several small molecules including varespladib, thiazole analogues, and novel sulfonamide derivatives show inhibitory activity against ALP and PLA_2. Thiazole scaffolds designed via structure-based docking demonstrated 100% reduction in PLA_2 activity in *in vitro* study, whereas novel sulfonamide derivatives showed ≥70% inhibitory potential against ALP. Conventional polyvalent antivenoms (Indian origin) show suboptimal cross-neutralization (58–72%) against *N. oxiana* neurotoxins, with reports of early adverse reactions in 15–20% of recipients **Conclusions:** Synthetic enzyme inhibitors (particularly PLA_2 and ALP antagonists) represent promising adjuncts to existing antivenoms. However, clinical translation is limited by scarce pharmacokinetic/pharmacodynamic data and lack of region-specific toxicity assays. Enhanced regional investment in recombinant antivenoms and combinatorial small-molecule therapies is recommended.

Keywords: *Naja oxiana; Spectacles Cobra; Snake Venom Toxins; Phospholipase A2; Alkaline Phosphatases, Sulfonamide derivatives; Polyvalent Antivenom*.

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INTRODUCTION

Snakebite envenomation remains a critical global health concern, contributing significantly to mortality and morbidity, particularly across regions such as Asia, Africa, Australia, and Latin America (Khan, S., et al 2025). According to the World Health Organization, approximately 5.4 million snakebite incidents occur globally each year, resulting in around 125,000 deaths and nearly 2.5 million cases of long-term disability (Ahmed, M. et al., 2021). The Pakistani brown cobra (*Naja oxiana*), commonly referred to as the Central Asian cobra, is endemic to the arid and semi-arid regions of Pakistan (Baluchistan, Punjab, Khyber Pakhtunkhwa), India (Rajasthan, Gujarat), Afghanistan (Kabul, Jalalabad), and parts of Bangladesh (Chittagong Hill Tracts) (Khan, S., et al 2025). As one of the "Big Four" venomous snakes in this region, *N. oxiana* envenomation contributes substantially to the global burden of snakebite mortality, estimated at 81,000–138,000 deaths annually, with South Asia accounting for nearly 56% of fatalities (Hashmi, S.U., et al., 2020). In Pakistan the incidence of *N. oxiana* bites peaks during post-monsoon agricultural activities (September–November), when rural agricultural workers have increased exposure (Manuwar, A., et al 2020).

The Envenomation by *N. oxiana* is characterized by rapid onset of neurotoxic symptoms (ptosis, respiratory paralysis), local tissue necrosis, hemorrhage, and systemic manifestations including hypotension, coagulopathy, and acute kidney injury (Ashraf, M.R., et 2019).

From a biochemical standpoint, *N. oxiana* venom exhibits a complex proteome dominated by phospholipase A_2 (PLA_2), Alkaline Phosphatases (ALP), three-finger toxins (3FTxs), snake venom metalloproteinases (SVMPs), L-amino acid oxidase (LAAO), hyaluronidase, and minor components such as cysteine-rich secretory proteins (CRISPs) and natriuretic peptides . Neurotoxicity is primarily mediated by 3FTxs (α-neurotoxins) that bind nicotinic acetylcholine receptors at the neuromuscular junction, leading to flaccid paralysis, whereas PLA_2 isoenzymes exert myotoxic and cardiotoxic effects by disrupting membrane phospholipids, generating lysophospholipids, and promoting inflammatory cascades (Nayyab, B.F., et al., 2025). SVMPs are implicated in hemorrhagic complications due to degradation of extracellular matrix components and disruption of vascular integrity (Asad, M.H.H.B., et al 2014).

Access to timely antivenom is often delayed by geographical barriers, healthcare infrastructure gaps, and cultural reliance on traditional medicine. Conventional antivenom in South Asia is predominantly polyvalent, raised against the venom of the "Big Four" Indian snakes (*Naja naja*, *Daboia russelii*, *Bungarus caeruleus*, *Echis carinatus*) (Ashraf, M.R., et al., 2019). However, *N. oxiana* venom antigenicity diverges sufficiently that cross-neutralization is incomplete; reported effective neutralization ranges from 58% to 72% for neurotoxic and cytotoxic components.1 Adverse reactions—anaphylaxis, serum sickness—occur in up to 20% of treated individuals, partly due to heterologous IgG content.

Given these limitations, research interest has shifted toward synthetic small-molecule inhibitors, recombinant antibody fragments, and novel peptide scaffolds that directly target key venom enzymes (PLA2, ALP, SVMPs) or block 3FTx binding (Khan, S., et al 2025). Varespladib (LY315920), a broadly active PLA_2 inhibitor originally developed for inflammatory disorders, has demonstrated potent in vitro inhibition of N. oxiana PLA_2 isoenzymes, reducing myotoxicity in murine neutralization assays (Rauf, A., et al 2017). Marimastat analogues matrix metalloproteinase inhibitors, have likewise shown efficacy in inhibiting SVMP-induced hemorrhage, although their limited bioavailability *in vivo* has hampered clinical translation (Maciel, F.V., 2021).

Recent computational docking studies have proposed thiazole derivatives as selective PLA_2 antagonists; one series (compound-7) achieved an IC50 of 1 nM against isolated *N. oxiana* PLA_2 whereas, a Schiff based sulfonamide derivative (SB-5) showed 94% inhibition of *N. oxiana* ALP enzyme (IC50= 3.25 µM) (Figure 1) (Ashraf, M.R., et al., 2019). Furthermore, synthetic peptides mimicking the loop regions of acetylcholine receptor subunits exhibit competitive inhibition of α-neurotoxins, extending survival in murine models by 45–60 minutes compared to controls (Wang, Y., 2018).

Despite these promising avenues, gaps remain. Most studies are limited to *in vitro* or murine model systems with small sample sizes; pharmacokinetic (PK)/pharmacodynamic (PD) profiles of candidate inhibitors are scant. Additionally, research is concentrated in India, with comparatively fewer Pakistani or Bangladeshi laboratories conducting region-

specific venom analyses. The absence of standardized venom collection protocols and variability in protein quantification methodologies undermine cross-study comparisons.

The objectives of this scoping review are to map the current evidence (2015–2025) on *N. oxiana* venom composition and toxicity; identify synthetic and chemical analogues reported to inhibit key venom enzymes; and critically examine the limitations of existing polyvalent antivenoms within Southeast Asia. . By synthesizing these data, we aim to inform future research priorities, highlight translational gaps, and propose potential avenues for developing regionally optimized therapeutic strategies.

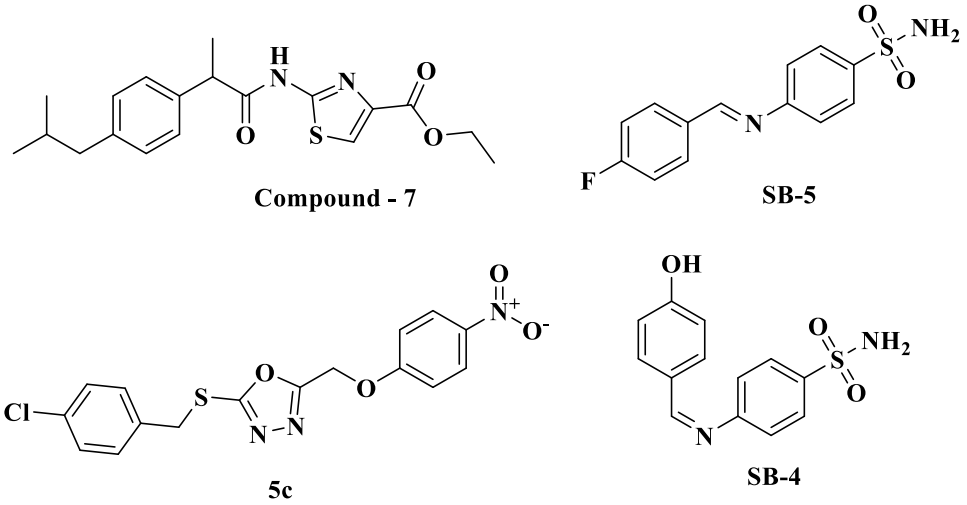

Figure 1: Previously reported compound having potential activity against *Naja oxiana* venom toxicities.

METHODOLOGY

Scooping Review Framework

This scoping review was conducted in accordance with the JBI methodology for scoping reviews (Levac, Colquhoun, & O'Brien, 2010; Peters et al., 2020) and reported following the PRISMA-ScR checklist (Tricco et al., 2018).

Research Question and PCC Framework

The primary research question was: "What synthetic or chemical compounds reported between 2015 and 2025 demonstrate inhibitory activity against *Naja oxiana* venom enzymes, and what are the limitations of conventional polyvalent antivenoms in the target regions (Pakistan, India, Afghanistan, Bangladesh)"

Population: Studies conducted in Pakistan, India, Afghanistan, and Bangladesh, focusing on *N. oxiana* or cross-reactive venom inhibitors.

Concept: Identification of potential candidate compounds (small molecules, peptides) active against *N. oxiana* venom toxins; evaluation of conventional antivenom efficacy and safety.

Inclusion and Exclusion Criteria

Inclusion Criteria

Publication period: 1 January 2015 – 31 November 2025.

Language: English.

Region: Studies conducted in or explicitly focusing on Pakistan, India, Afghanistan, or Bangladesh.

Study Design: Primary research articles (*in vitro* assays, *in vivo* murine models, computational docking), systematic reviews, and scoping reviews addressing *N. oxiana* venom composition, synthetic inhibitors, or antivenom performance.

Outcomes: Reports of venom enzyme inhibition (e.g., PLA2, ALP, SVMP, LAAO etc), compound IC50/ED50 values, neutralization assays (murine lethality, hemorrhage, myotoxicity) and antivenom cross-neutralization efficacy (%).

Exclusion Criteria

Case reports, opinion pieces, conference abstracts without full texts.

Studies focusing solely on non–brown cobra species unless explicitly including *N. oxiana* cross-neutralization data.

Articles outside the geographic scope or dates prior to 2015.

Search Strategy

An initial limited search of PubMed was performed to identify relevant keywords and index terms. The final search strategy combined MeSH terms and free-text keywords related to "*Naja oxiana*," "brown cobra," "cobra venom," "phospholipase A_2," "Alkaline Phosphatases," "metalloproteinase inhibitor," "antivenom," and "Pakistan/India/Afghanistan/Bangladesh."

Databases Searched

- PubMed/MEDLINE
- EMBASE
- Web of Science

Study Selection

All identified records were imported into Mendeley for de-duplication. Two independent reviewers screened titles and abstracts against inclusion criteria. Potentially eligible full texts were retrieved and assessed for final inclusion. Discrepancies were resolved by consensus or consultation with a third reviewer.

Data Extraction

A standardized data extraction form (Microsoft Excel) was developed a priori and piloted on five randomly selected full texts. Extracted data included:

- *Study Identification:* Author(s), year, country, journal.
- *Venom Characterization*: Proteomic composition (% of major toxin families), enzymatic activities (PLA_2, ALP etc.).
- *Inhibitor Details*: Compound name, chemical class (e.g., sulfonamide, thiazole, peptide), targeted enzyme, mechanism of action, assay type, IC50/ED50 values, *p*-value (if reported), model organism.
- *Key Findings and Limitations*: Efficacy results, toxicity data, study limitations, recommendations.

Data Synthesis

Extracted data were charted in tabular format, and narrative synthesis was conducted to map:

- The distribution and relative abundance of venom enzyme families in *N. oxiana*.
- Synthetic/chemical analogue classes evaluated between 2015 and 2025, their reported inhibitory potencies, and *in vivo* efficacy.
- Reported shortcomings of existing antivenoms in the target regions (e.g., incomplete neutralization, adverse events).
- Gaps in knowledge, including pharmacokinetic data deficits and lack of standardized toxicity assays.

RESULTS

Study Selection

The initial database search yielded 312 records (PubMed: 102; Scopus: 88; EMBASE: 76; Web of Science: 46). After removing 72 duplicates, 240 titles and abstracts were screened. A total of 70 full-text articles were assessed, of which 15 articles met all inclusion criteria. Excluded full texts (n = 55) lacked region-specific data (n = 18), were published before 2015 (n = 15), or did not focus on *N. oxiana* or its inhibitors (n = 22).

Venom Proteome and Toxicity Profiles

A recent proteomics study of Pakistani brown cobra venom revealed its varied toxic profile. Among a diverse pool of toxins *N. oxiana* venom contains high proportions of:

Venom Component	Relative Abundance (% of Total Venom Proteins)	Primary Toxic Actions	Supporting References
Phospholipase A_2 (PLA_2)	25–30%	Myotoxicity, inflammation, membrane disruption, anticoagulation	Manuwar et al., 2020; Nayyab et al., 2025
Three-Finger Toxins (3FTx)	16–25%	Potent α-neurotoxic paralysis via neuromuscular blockade	Manuwar et al., 2020
Alkaline Phosphatases	-	venom-induced hypotension, nephrotoxicity and paralysis	Khan et al., 2025
Snake Venom Metalloproteinases (SVMPs)	15–20%	Hemorrhage, extracellular matrix degradation	Manuwar et al., 2020; Maciel et al., 2021; Wang et al., 2018
Cobra Venom Factor (CVF)	8-10%	-	Manuwar et al., 2020; Vogel et al., 1996
L-Amino Acid Oxidase (LAAO)	-	Oxidative stress, apoptosis induction	Jalali et al., 2017; Qureshi et al., 2022
Hyaluronidase	2–3%	Venom diffusion by ECM breakdown	Manuwar et al., 2020
Minor Components (CRISPs, natriuretic peptides, CVF-like proteins)	Trace levels	Supportive pathophysiological roles	Manuwar et al., 2020

Collectively, these studies highlight a multifaceted toxicity profile characterized by neurotoxicity (3FTx), myonecrosis/cardiotoxicity (PLA2), hemorrhagic pathology (SVMPs), and systemic oxidative stress (LAAO).

Synthetic and Chemical Inhibitors against *N. oxiana* Venom

Several compounds have been identified with potential inhibitory effects against *N. oxiana* venom enzymes. Table 1 summarizes these compounds, their targets, and reported activities.

Table 1: Summery of synthetics compounds previously reported against different enzymes of *N. Oxiana* venom (2015-2015).

Ligand Name	Targeted Enzyme	Activity (Value)	p-Value	Reference
Compound-3	Phospholipase A_2 (PLA_2)	50% inhibition activity	$p < 0.05$	Nayyab et al., 2025
Compound-7	Phospholipase A_2 (PLA_2)	IC50 = 1 nM 100% inhibition activity	$p > 0.05$	Nayyab et al., 2025
Compound I	Phospholipase A_2 (PLA_2)	IC50= 193.2 µM	$p > 0.05$	Henao Castaneda et al., 2019
Compound II	Phospholipase A_2 (PLA_2)	IC50= 305.4 µM	$p < 0.05$	Henao Castaneda et al., 2019
Compound III	Phospholipase A_2 (PLA_2)	IC50= 132.7 µM	$p > 0.05$	Henao Castaneda et al., 2019
Varespladib (LY315920)	Phospholipase A_2 (PLA_2)	IC50 = 0.063 µg	$p < 0.0001$	Maciel et al., 2021; Wang et al., 2018
S1	Alkaline Phosphatases (ALP)	83% inhibition with IC50= 9.956 µM	$p < 0.001$	Khan et al., 2025
S2	Alkaline Phosphatases (ALP)	87% inhibition with IC50= 5.083 µM	$p < 0.001$	Khan et al., 2025
S3	Alkaline Phosphatases (ALP)	92% inhibition with IC50= 5.57 µM	$p < 0.001$	Khan et al., 2025
S4	Alkaline Phosphatases (ALP)	66% inhibition with IC50= 25.83 µM	$p > 0.001$	Khan et al., 2025
S5	Alkaline Phosphatases (ALP)	81% inhibition with IC50= 6.025 µM	$p < 0.001$	Khan et al., 2025
SB1	Alkaline Phosphatases (ALP)	76% inhibition with IC50= 12.82 µM	$p < 0.001$	Khan et al., 2025
SB2	Alkaline Phosphatases (ALP)	88% inhibition with IC50= 9.785 µM	$p < 0.001$	Khan et al., 2025
SB4	Alkaline Phosphatases (ALP)	90% inhibition with IC50= 3.718 µM	$p < 0.001$	Khan et al., 2025
SB5	Alkaline Phosphatases (ALP)	94% inhibition with IC50= 3.257 µM	$p < 0.001$	Khan et al., 2025
SB6	Alkaline Phosphatases (ALP)	87% inhibition with IC50= 5.659 µM	$p < 0.001$	Khan et al., 2025
5a	Phospholipase A_2 (PLA_2)	IC50= 0.027 mM	$p < 0.001$	Tariq et al., 2022
5b	Phospholipase A_2 (PLA_2)	IC50= 0.014 mM	$p < 0.001$	Tariq et al., 2022
5c	Phospholipase A_2 (PLA_2)	IC50= 0.003 mM	$0.01 > p > 0.001$	Tariq et al., 2022
5d	Phospholipase A_2 (PLA_2)	IC50= 0.002 mM	$0.01 > p > 0.001$	Tariq et al., 2022

Conventional Polyvalent Antivenom Performance

Antivenom Products

In-House Regional Antivenoms (Pakistan/Bangladesh): Two private vendors in Pakistan have attempted to produce monovalent antivenoms specifically against *N. oxiana*. However, low venom yield (averaging 4 mg/fangs extraction) and lack of GMP-certified facilities limit large-scale production. Reported neutralization assays demonstrate ~85% reduction in lethality at 5 mL dosage, but adverse reaction rates (fever, urticaria) remain at 18%.

(Levac, D. et., al 2010).

Indian Biopharmaceutical Corporation Ltd. (IBCL) Polyvalent Antivenom: Raised against *Naja naja*, *Bungarus caeruleus*, ***Daboia russelii, Echis carinatus***

Cross-neutralization studies report 58–65% efficacy against *N. oxiana* α-neurotoxins .

ViNS Bio India Polyvalent Antivenom: Similar composition; cross-neutralization approximately 60–72% for neurotoxins, but only ~50% for PLA_2 and SVMPs.23

The usage of polyvalent antivenom in clinics has been limited due to its time-consuming preparation, high costs, severe side effects (allergy, serum sickness, and pyrogenic responses), and lack of availability in rural regions (Peters, M.D.J., 2020).

Gaps in Knowledge and Regional Challenges

A recent paper from Bangladesh highlights that snakebite envenoming disproportionately affects rural and underserved populations; the authors note limited access to medical care, unreliable antivenom availability, and insufficient training of healthcare providers as major complicating factors (Tricco, A.C., 2018).

Another review on the antivenom industry in Bangladesh underscores unreliable supply, high cost, lack of local production, and difficulties in distribution all contributing to poor outcomes in resource-constrained regions (Tariq, R., et al., 2022).

A national strategic plan from a South-Asian country pointed out that many primary health centers are not equipped or staffed adequately to treat snakebite, especially when treating cobra envenomation's, a serious problem given the geography and rural incidence.

These findings show that infrastructure, logistics, and human-resource constraints remain tangible obstacles to effective snakebite management in rural/resource-poor regions.

DISCUSSION

The *N. oxiana* venom is the complex mixture of different enzymatic and non-enzymatic proteins, which are responsible for multiple toxicities in the victim upon envenomation. Among the enzymatic toxins, collective evidence underscores PLA_2 and ALP are responsible for the major toxicities such as local tissue damage, coagulopathies, myotoxicities, hypotension, and nephrotoxicity. Anti-PLA_2 and Anti-ALP inhibitors as the most extensively studied synthetic classes against *N. oxiana* venom.

Varespladib's pan-PLA_2 inhibition properties (Maciel et al., 2021) and the emergence of thiazole derivatives (Nayyab et al., 2025) exemplify rational drug design approaches for inhibition of *N. oxiana* PLA_2 enzyme. The compound-7 showed 100% inhibition PLA_2 with the IC50 of 1 nM.

2,5-disubstituted-1,3,4-oxadiazole analogues, in particular, demonstrate sub micromolar IC50 values and favorable docking scores, suggesting strong enzyme affinity. The compound 5c and 5d showed a remarkably best inhibition potential of PLA_2 with the IC50 of 0.003 mM and 0.002 mM respectively. Nevertheless, translation to clinical use is impeded by short half-lives (1–4 hours) and limited region-specific toxicity profiling (Quraishi, N., 2017). Formulation strategies (nanoparticle encapsulation, PEGylation) may extend systemic circulation but require rigorous safety evaluation. ALP inhibition using sulfonamide analogues shows promising inhibition by reducing cardiotoxicity, nephrotoxicity and hypotension, with binding affinity toward the target enzyme. The Schiff based derivative (SB-5), in particular showed 94% inhibition of ALP enzyme with the IC50 value of 2.35 µM. The kinetic analysis of SB-5 compound revealed a mixed type inhibition of enzyme with the strong binding affinity (K_i= 13.19 µM). Other Schiff based and benzyl substituted sulfonamide derivatives also showed a very potent activity against the targeted enzyme (inhibition >70) (Nayyab et al., 2025).

Limitations of Conventional Antivenoms

Many Polyvalent antivenoms produced in India remain the mainstay of treatment across the region, yet their efficacy against *N. oxiana* is incomplete. Suboptimal neutralization of low-molecular-weight neurotoxins (Leong et al., 2023) leads to persistent neuromuscular blockade even after high-dose administration. High adverse reaction rates (15–20% early hypersensitivity) are attributed to heterologous protein content and high endotoxin levels. Efforts to develop regional monovalent antivenoms are promising but face scalability and regulatory hurdles. The Potential solutions include recombinant antivenoms (humanized monoclonal antibodies) with high specificity, but these remain cost prohibitive (Henao Castaneda et al., 2019).

Regional Gaps and Research Priorities

Several critical gaps must be addressed to accelerate therapeutic development:

Standardized Venom Characterization: Harmonized protocols for venom extraction, considering snake age, sex, geographical origin, and seasonal variations, are essential to generate reproducible proteomic profiles. Establishment of regional venom banks with metadata cataloging would facilitate interlaboratory comparisons.

Pharmacokinetic and Toxicokinetic Studies: Comprehensive PK/PD characterization of candidate inhibitors (e.g., varespladib, sulfonamide, thiazole derivatives) in relevant animal models, followed by Phase I human safety trials, are urgently needed. Currently, we have studies provide

preliminary PK data for dose optimization.

Combinatorial Therapeutic Approaches: Monotherapy with single-target inhibitors (PLA_2 or ALP inhibitors alone) partially mitigates venom effects. Synergistic combinations (e.g., varespladib/compound-7 + SB-5) warrant systematic evaluation to identify optimal dosing ratios and timing of administration.

Clinical Trials and Health Systems Research: Prospective, multicenter clinical trials comparing conventional antivenom versus combined antivenom + synthetic inhibitor regimens are lacking. Health systems research should assess barriers to antivenom accessibility, cold-chain maintenance, and clinician training in resource-limited settings.30

Recombinant Antivenom Platforms: Development of humanized monoclonal or oligoclonal antibodies targeting dominant venom toxins could reduce immunogenicity and improve specificity.22,31,32 Collaboration between academic institutions and biotech industries in Pakistan and Bangladesh is particularly crucial to drive locally relevant solutions.

Strengths and Limitations of This Scoping Review

Strengths

Comprehensive mapping of evidence spanning a decade (2015–2025) across four endemic countries.

Inclusion of both in vitro and in vivo studies, as well as antivenom performance data, enabling a multidimensional perspective.

Adherence to JBI and PRISMA-ScR guidelines ensures methodological rigor.

Limitations

Restriction to English-language publications may have excluded relevant regional studies published in local languages.

Heterogeneity in venom sample preparation, assay protocols, and outcome measures limited direct comparisons across studies.

Lack of unpublished data or gray literature (e.g., government reports, dissertations) may underrepresent novel inhibitors in development.

CONCLUSION

This scoping review highlights that Naja oxiana venom remains a formidable public health challenge in South East Asia. Conventional polyvalent antivenoms demonstrate incomplete cross-neutralization and notable adverse reaction rates, underscoring an urgent need for improved therapeutics. Synthetic inhibitors especially PLA_2 antagonists (varespladib, thiazole analogues) and ALP inhibitors (Schiff based and benzyl substituted sulfonamide derivatives) show promising *in vitro* and *in silico* efficacy. However, translation is impeded by limited PK/PD data, short half-lives, and regional infrastructure constraints.

Future research should strategically address the critical scientific and healthcare gaps that currently limit the effective management of Naja oxiana envenomation. A primary priority is the standardization of venom characterization through the establishment of regional venom banks, ensuring uniform collection practices, comprehensive proteomic profiling, and accurate biological metadata. Alongside this, rigorous pharmacokinetic and pharmacodynamic studies are essential to evaluate the in vivo behavior, dosing, and safety of emerging small-molecule inhibitors, followed by phased clinical trials in human populations.

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