

Effects of Snake Venom and Antivenom on the Immune Response: A Literature Review

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ARTICLE INFO

Keywords: Venomous Snake Bites, Envenomation, Immune Reactions, Antivenom, And Inflammation.

Received : 27, April

Revised : 29, May

Accepted: 30, June

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ABSTRACT

In tropical countries, including, Indonesia, venomous snake bites remain a significant public health problem. Through the activation of proinflammatory cytokines, the complement system, and oxidative stress, envenomation can cause tissue damage and systemic complications. Antivenom is the primary method for neutralizing toxins, but its heterologous immunoglobulin content can trigger immune reactions. This study examines how snake venom and antivenom affect the immune system. A total of 19 articles from a literature review published between 2020 and 2026 were evaluated using narrative synthesis. Data were collected from SINTA-indexed national journals, PubMed, ScienceDirect, and Google Scholar. The results show that snake venom can cause local and systemic inflammation, while antivenom can cause hypersensitivity and even serum sickness. To improve the safety and effectiveness of therapy, antivenom remains the primary choice. However, monitoring for immunological risks is necessary

INTRODUCTION

One public health issue that remains a global concern, particularly in tropical and subtropical countries, is venomous snake bites. Millions of snake bite cases occur worldwide each year, causing significant social, economic, and health impacts on affected communities. Consequently, this condition has been classified as a neglected tropical disease (NTD) due to its high incidence, mortality, and disability rates, particularly among populations living in rural areas with limited access to healthcare (Dias et al., 2023).

Many snake species from the families Viperidae and Elapidae (Gabrili et al., 2022) inhabit various regions of Indonesia and frequently interact with humans in agricultural areas, plantations, and settlements located near snake habitats. This is due to the high diversity of snake species in Indonesia. Furthermore, limited access to antivenom in some areas remains a challenge in managing envenomation cases and can increase the risk of complications and death (Simangunsong et al., 2024).

Snake envenomation is a condition caused by the entry of snake venom into the human body through a bite, leading to various biological complications. Snake venom consists of a combination of proteins, peptides, enzymes, and other bioactive molecules with high pharmacological activity. Phospholipase A2 (PLA2), snake venom metalloproteinase (SVMP), serine proteases, L-amino acid oxidase (LAAO), and various types of neurotoxins are the main components frequently found. These components can cause various clinical manifestations, including coagulation problems, bleeding, tissue necrosis, muscle damage, acute kidney failure, and life-threatening respiratory distress (Guidolin et al., 2023).

Snakes can disrupt the immune system in addition to causing direct toxic effects. Snake components can activate the complement system, stimulate the release of proinflammatory cytokines, and trigger an inflammatory response that leads to tissue damage and systemic complications. Activation of the immune system can help eliminate toxins, but an excessive response can actually worsen the patient's clinical condition by increasing vascular permeability, endothelial damage, and inflammation (Gabrili et al., 2022).

To date, snake antivenom remains the primary specific treatment for snakebites. Antivenom binds to and neutralizes the toxic components of snake venom, which can reduce symptoms and mortality rates. The match between the type of antivenom and the species of snake responsible for the bite, the timing of administration, and the patient's clinical condition significantly influence the effectiveness of the treatment (Dias da Silva et al., 2022).

Although antivenoms are highly beneficial, their use can cause various immune reactions. This is because most antivenom products are derived from heterologous animal immunoglobulins. Early hypersensitivity reactions, such as urticaria, bronchospasm, and anaphylaxis, as well as delayed reactions, such as serum sickness caused by the formation of immune complexes, can lead to more serious complications, such as vasculitis, glomerulonephritis, and reactive arthritis (Pineda & Ra, 2025).

The success of therapy depends not only on the ability to neutralize toxins, but also on the management of the immune response that arises during

treatment. This is demonstrated by the complexity of the interactions between the toxic effects of snake venom and the immune response to antivenom. In addition, previous studies have shown that there are differences in the immune response influenced by different snake species, toxin composition, antivenom characteristics, and the patient's clinical condition. Antivenom is a specialized medication that is highly effective in eliminating snake toxins and reducing morbidity and mortality resulting from envenomation. However, the use of antivenom can cause various immune reactions, such as immediate hypersensitivity and serum sickness caused by the formation of immune complexes. These conditions indicate that the success of snake bite therapy depends on the antivenom's ability to neutralize toxins and how the immune system optimally manages snake venom and antivenom. Therefore, understanding how snake venom interacts with antivenom and the immune system is crucial for improving the safety and efficacy of envenomation therapy (Dias da Silva et al. 2022).

Snake venom toxicity, antivenom efficacy, and the clinical signs of envenomation have all been discussed in various previous studies. However, research examining the impact of snake venom on the immune system and the effects of antivenom administration on the immune system remains very limited. In addition, immune responses vary depending on snake species, toxin composition, antivenom properties, and patient conditions, all of which are not yet fully understood. Based on this situation, this study provides an update by using an integrative approach that examines the relationship between snake venom, antivenom, and the body's immune response. This study is based on the latest literature from 2020–2026. It is hoped that this study will enhance our understanding of how the immunopathology of envenomation occurs and assist in the development of safer and more effective antivenom therapies. Therefore, the objective of this study is to investigate how snake venom and antivenom influence the body's immune response and how this impacts the development of safer and more effective therapies in the future. Therefore, to improve the safety and efficacy of envenomation therapy, it is crucial to understand the immunological mechanisms involved. Various studies have addressed snake venom toxicity, the mechanisms of action of antivenoms, and the clinical manifestations of envenomation. However, research specifically examining the relationship between the immunological effects of snake venom and the immune response induced by antivenom administration remains relatively limited. Previous studies have largely focused on toxicological aspects, the clinical efficacy of antivenoms, or specific immunological side effects. Therefore, the objective of this study is to investigate the effects of snake venom and antivenoms on the body's immune response and their implications for the development of safer and more effective therapies in the future (Dias da Silva et al., 2022)

THEORITICAL REVIEW

The Immune System and Snake Bites

The body's defense system protects the body from various foreign substances, such as toxins, microorganisms, and other harmful substances. The immune system consists of two main parts: the innate immune system and the adaptive immune system. The innate immune system serves as the first line of defense by activating the complement system, dendritic cells, macrophages, and neutrophils. Additionally, T lymphocytes and B lymphocytes are part of the adaptive immune system, which is responsible for generating specific immune responses and maintaining immune memory. When the body recognizes an antigen or foreign substance, the immune system is activated. In this process, various inflammatory mediators, including cytokines, chemokines, and growth factors, are released; growth factors regulate the body's defense response. Although the immune system is vital for protecting the body, overactivating it can lead to tissue damage and disruption of organ function (Gabrili et al., 2022).

Snake venom originates from venom glands and consists of a complex mixture of proteins, peptides, enzymes, and bioactive molecules. The main components of snake venom include phospholipase A2 (PLA2), snake venom metalloproteinase (SVMP), serine proteases, hyaluronidase, neurotoxins, hemotoxins, and cytotoxins. Each component has a unique mechanism of action. Neurotoxins cause paralysis and disrupt nerve transmission, hemotoxins interfere with the blood clotting system, and cytotoxins damage local tissues. In addition to these harmful direct effects, snake venom components can also activate the immune system and trigger inflammatory reactions that promote the progression of envenomation (Guidolin et al., 2023).

The immune system recognizes a snake entering the body as a foreign substance. In this process, various immune cells are activated and release inflammatory mediators such as TNF- α , IL-1 β , and IL-6, which cause increased blood vessel permeability, edema, and tissue damage. Additionally, snake bites have the potential to activate the complement system, which produces various pro-inflammatory mediators. The effects of the toxin directly influence the clinical manifestations of a snake bite, but activation of the complement system can also exacerbate tissue damage if it occurs excessively (Gabrili et al., 2022).

Antivenoms are specialized medications used to neutralize toxins in snake venom. Antivenoms are made from immunoglobulins derived from animals that have been immunized with snake venom and are administered to patients. Once administered, antivenoms bind to the toxins, preventing them from interacting with their biological targets. Although antivenoms are effective, they can cause immune reactions because the human body recognizes their heterologous proteins as antigens. Early hypersensitivity, anaphylaxis, and serum sickness are some of the reactions that may occur (Patel et al., 2021). Therefore, understanding how snake venom, antivenom, and the immune system interact with one another is crucial for improving the safety of therapy.

Various studies have shown that the envenomation process involves not only the direct toxic effects of snake venom components but also activates the immune system, leading to tissue damage and systemic complications. Complement system activation, the release of pro-inflammatory cytokines, and

an excessive inflammatory response are key factors in the development of tissue damage and systemic complications. On the other hand, antivenom serves as the primary therapy for envenomation (Gabrili et al., 2022).

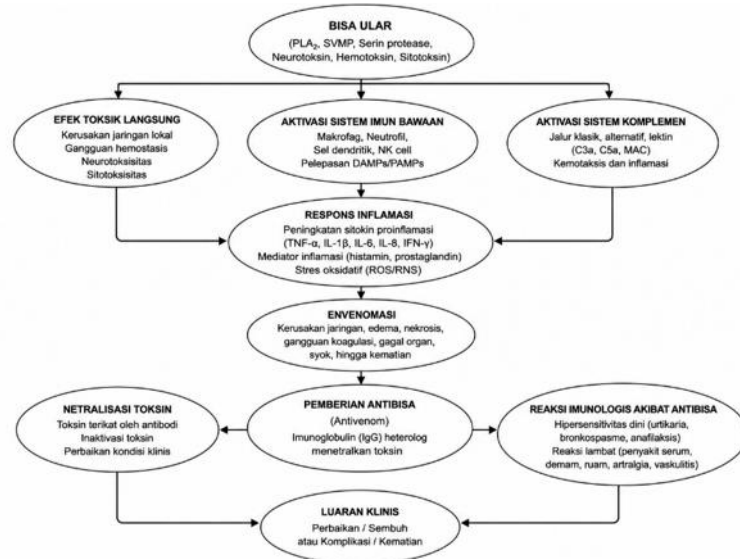


Figure 1. Conceptual Framework of the Interaction Between Snake Venom, the Immune System, and Antivenom in Venomous Snake Bites

METHODOLOGY

This study explores the relationship between snake venom, antivenom, and their effects on the immune system. A comprehensive literature review was conducted using several electronic databases, such as Google Scholar, PubMed, and ScienceDirect, as well as national journals indexed in SINTA. These databases were selected due to their extensive coverage of publications and their relevance to the fields of pharmacy, toxicology, immunology, and clinical medicine, ensuring they provide credible and up-to-date scientific information.

To improve the sensitivity and specificity of the search, English keywords such as “snake venom,” “envenomation,” “antivenom,” “immune reaction,” “hypersensitivity,” “anaphylaxis,” “serum sickness,” and “immune reaction” were used to search for publications from 2020 to 2026. Additionally, to identify supporting supplementary sources, a search was also conducted through the reference lists of relevant articles.

The articles included were preclinical and clinical research articles that were available in full and related to the immune mechanisms triggered by snake venom and antivenom administration. The analysis excluded articles that were irrelevant to the research topic, duplicates, incomplete, or not supported by empirical data. To ensure that the articles align with the research objectives, the article selection process was conducted in stages. It began with an initial search, followed by selection based on titles and abstracts, and finally, a comprehensive evaluation of the article content.

Next, the data obtained were analyzed using a qualitative descriptive method with a narrative synthesis approach. This analysis was conducted by

comparing and integrating findings from various sources to gain a better understanding of the relationship between snake venom, antivenom, and the body's immune response. The results of the analysis are presented in narrative form and in tables based on the main themes: types of snake venom, mechanisms of toxicity, and types of snake venom.

To ensure transparency and systematicity in the process of identifying, screening, assessing the eligibility of, and including articles used in the study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were applied. All articles meeting the inclusion criteria were subsequently evaluated based on topic relevance, research methodological quality, and their role in enhancing our understanding of the relationship between snake venom, antivenom, and the body's immune response.

RESEARCH RESULTS

A literature review revealed that 19 articles met the criteria and were included in the final analysis; these included 7 preclinical research articles and 12 clinical research articles, as well as several other supporting studies relevant to the research topic (Figure 1). Various types of research, including experimental and observational studies, as well as case reports, are discussed in this article. This study discusses the effects of snake venom, the mechanism of action of antivenoms, and the immune response they elicit (Table 1).

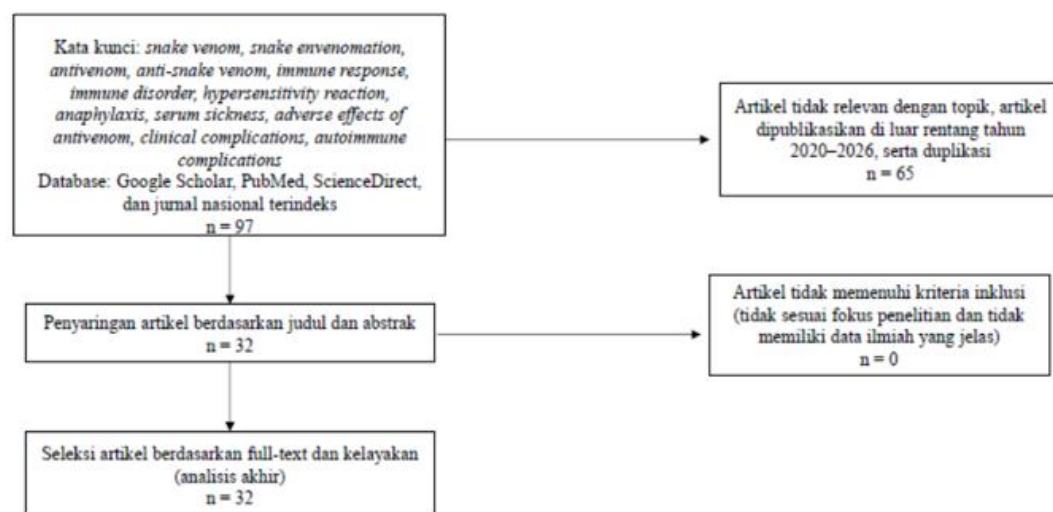


Figure 1. PRISMA Flowchart for the Literature Selection Process

Based on the study findings, envenomation occurs because snake venom contains various bioactive molecules, such as phospholipase A2, metalloproteinases, and neurotoxins. These molecules damage tissues and activate the immune system through the release of inflammatory mediators. Both local effects and severe systemic complications are among the clinical manifestations caused by this activity. These findings indicate a consistent pattern in determining the severity of a patient's envenomation.

Table 1. Research Characteristics

Snake		Research Location and Type	Characteristics of the Snake	Toxic Effects and Complications	Mechanism of Toxicity	Snake antivenom (type)	Library
Genus	Species						
Preclinical							
Bothrops	B. lanceolatus	Prancis (Caribbean research / French territories) – review & experimental immunopathology	PLA2, SVMP, serine protease	Thrombosis, systemic inflammation	Complement activation & vascular inflammation	Antivenom polivalent IgG/F(ab') ₂	Gabrili et al., 2023
Bothrops	B. lanceolatus	Costa Rica / Latin America – in vivo murine thromboinflammatory model	Complex viperid toxin	Emboli, koagulopati	Activation of coagulation and systemic inflammation	Antivenom polivalent	Guidolin et al., 2023
Bothrops	B. lanceolatus	Martinique (French Caribbean) – in vitro & ex vivo human blood study	PLA2 + aktivator komplemen	Hemolisis, inflammasi berat	Disrupsi membran & aktivasi komplemen	Antivenom Bothrops	Dias da Silva et al., 2022
Bothrops	B. jararaca	Brasil – in vitro human whole blood study	Metalloproteinase, PLA2	Edema, nekrosis	Aktivasi sistem komplemen	Antivenom Bothrops (F(ab') ₂)	Gabrili et al., 2022
-	Model murine	Global (laboratory study) – in vivo murine acute	PLA2, LAAO	Inflammasi sistemik	Aktivasi sitokin fase akut	Antivenom IgG	Alsolaiss et al., 2022

Snake		Research Location and Type	Characteristics of the Snake	Toxic Effects and Complications	Mechanism of Toxicity	Snake antivenom (type)	Library
Genus	Species						
Pseudochis	P. porphyriacus	phase response Australia – in vitro venom proteomic & immunological study	α -neurotoxin, PLA2, myotoxin	Paralysis, immunosuppression	Neuromuscular block & immunomodulation	Antivenom elapid monovalent	Ryan et al., 2020
Not specific	-	Pre-clinical experimental	Pharmacokinetics of antivenom	Distribution	ADME	Antivenom	Herrera-Vara et al., 2026
Not specific	-	Klinis India – Case report	Immune response to antivenom	Hypersensitivities	IgE mediated hypersensitivity	Antivenom	Patel et al., 2021
Bothrops	Spp	Uruguay – Retrospective clinical analysis	Hemotoxin (SVMP, PLA2, serine protease)	Side effects of antivenom	Inflammatory and complement activation	Antivenom	Negrin et al., 2021
Not specific	-	India – Case report	Antigen-based antivenom	Anaphylaxis	Hypersensitivity tipe I	Antivenom	Feng et al., 2022
Porthidium	Ophryomorphs	Latin America – Case report	Hemotoxin (SVMP, PLA2)	Serum sickness	Immune complex (type III) hypersensitivity)	Antivenom	Pineda & Ra, 2025
Not specific	-	China – Data analysis poison center	Antivenom immune response	Early reaction	Activation of the innate immune system	Antivenom	Sriphana et al., 2022

Snake		Research	Characte	Toxic	Mechanis	Snake	Library
Genus	Spesie s	Location and Type	ristics of the Snake	Effects and Compli cations	m of Toxicity	antiveno m (type)	
Not specif ic	-	India - Case report	Protein antiveno m	Anafila ksis	Histamin release	Antivenom	Rajdan et al., 2023
Naja	Spp	India - Observasi onal	Neuroto ksin (α - neurotox in, PLA2)	Paralisi s	Blokade reseptor Ach	Antivenom	Ahma d & Rehatt a, 2024
Not specif ic	-	Indonesia - Analisis	Ketersed iaan antiveno m	Mortalit as	Akses layanan kesehata n	Antivenom	Siman gunso ng et al., 2024
Bitis	Arieta ns	Afrika - Eksperime ntal	Hemoto ksin (SVMP, PLA2)	Nekrosi s jaringan	Proteolisi s	Antivenom	Alsolai ss et al., 2022
Multi- specie s	-	Global - Review	Herbal compou nds vs. venom	Alternat ive therapy	Inhibisi enzim venom	Herbal/an tivenom	Dias et al., 2023
Gloyd ius	Spp	Korea Selatan - Retrospekt if	Hemoto ksin (PLA2, protease)	Koagul opati	Coagulati on disorders	Antivenom	Khoch are et al., 2023
Callos elasm a	Rhodo stoma	Vietnam - Case Study	Hemoto ksin (SVMP, PLA2)	Variasi respon klinis	Antigen variabilit y	Antivenom	Le et al., 2025

Notes: PLA2 = phospholipase A2; SVMP = snake venom metalloproteinase;
LAAO = L-amino acid oxidase; SABU = Snake Venom Antiserum.

According to preclinical studies, snake venom components have the ability to trigger inflammatory reactions by increasing proinflammatory cytokines and activating the complement system, which is responsible for tissue damage. The hemotoxic effects of Viperidae snakes, such as Bothrops, involve coagulation disorders, vascular damage, and inflammation. An excessive immune response to this condition can worsen the patient's condition by increasing vascular permeability and activating inflammatory mediators.

Additionally, toxins from species such as *Pseudechis porphyriacus* can affect the immune system, resulting in various inflammatory responses (Patel et al., 2021). In clinical studies, envenomation by species of the Elapidae family, such as *Naja kaouthia*, has a more pronounced neurotoxic effect, leading to paralysis and respiratory distress (Gabrili et al., 2022). Secondary inflammatory mechanisms exacerbate the clinical condition through the immune response, although the primary effect is neurotoxic. These different types of clinical manifestations indicate that the patient's condition and the snake species significantly influence the body's response to snake venom (Ahmad & Rehatta, 2024).

Antivenom is the primary treatment for snakebites and works by neutralizing toxins through antigen-antibody interactions. Clinical studies show that the compatibility between the type of antivenom and the venom composition of the snake species involved significantly affects the antivenom's effectiveness. Additionally, the use of antivenom has been shown to reduce mortality, although its side effects still require careful consideration.

One important aspect of clinical research is the immune response to antivenom administration. Activation of the immune system, as indicated by the release of histamine from mast cells, often leads to immediate hypersensitivity, which can result in more severe reactions such as anaphylaxis requiring immediate treatment. The formation of immune complexes that cause systemic inflammation can also lead to delayed reactions such as serum sickness. In addition, clinical studies have shown that the dose, frequency of administration, and the patient's clinical condition influence the frequency and severity of reactions to antivenoms. The use of antivenoms in certain conditions, such as coagulation disorders, sometimes requires close monitoring to prevent additional complications. Furthermore, differences in the composition of antivenoms affect the safety and efficacy of therapy.

Overall, a review of 19 articles indicates that snake venom serves two functions: as a toxic substance that damages tissue and as a catalyst for a complex immune response. Antivenom, on the other hand, serves as the primary treatment for neutralizing toxins, but it also has the potential to trigger harmful immune reactions. This suggests that the success of therapy depends on the ability to eliminate toxins and control the patient's immune response. Consequently, antivenom must be administered appropriately, weighing therapeutic benefits against the risk of side effects. To develop safer and more effective antivenom therapies in the future, a deeper understanding of immunological mechanisms is required.

DISCUSSION

The Effects of Snake Venom on the Immune Response

The diverse bioactive components of snake venom include phospholipase A2 (PLA2), snake venom metalloproteinase (SVMP), serine proteases, and neurotoxins, each of which has toxic and immunological effects (Rajdan et al., 2023). These components have the ability to activate the complement system and stimulate the release of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α); leading to

inflammatory reactions occurring at both the local and systemic levels (Gabrili et al., 2022).

Inflammatory activation increases blood vessel permeability, leading to edema, infiltration of inflammatory cells, and tissue damage at the bite site. A more severe inflammatory response can lead to coagulation disorders, tissue necrosis, organ damage, or multi-organ failure. Therefore, the clinical symptoms resulting from a snake bite are influenced by both the toxic effects and the immune response following envenomation (Gabrili et al., 2023).

The Immune System's Response to Antivenom

Antivenoms neutralize toxins through the antigen-antibody binding mechanism. Administration of antivenom immediately after a venomous snake bite has been shown to reduce symptoms, halt further tissue damage, and reduce mortality from venomous snake bites (Dias da Silva et al. 2022).

However, since most antivenom products are derived from animal immunoglobulins, their use can trigger immune reactions. The most common reactions include immediate hypersensitivity reactions such as urticaria, pruritus, bronchospasm, and anaphylaxis, which can occur within minutes to several hours after antivenom administration. Additionally, the formation of immune complexes can cause a delayed reaction known as serum sickness, which typically appears several days after treatment (Patel et al., 2021).

The Impact and Development of Antivenoms

The development of safer antivenoms is driven by the potential for immunological reactions caused by antivenoms. According to several studies, the use of modern purification technologies can reduce the risk of hypersensitivity by lowering the levels of nonspecific proteins. The development of antibody fragments and monoclonal antibodies is also a promising method for enhancing toxin neutralization efficacy with lower immunogenicity (Negrin et al., 2021). This study found that snake venom and antivenom are linked to the immune system. Snake venom activates various inflammatory mechanisms that cause tissue damage and systemic problems, while antivenom is capable of neutralizing toxins but has the potential to trigger an immune response. Therefore, understanding how snake venom, antivenom, and the immune response interact is crucial for developing safer and more effective treatments in the future.

Efforts to Develop Safer and More Effective Antivenoms

Despite the fact that antivenom remains the primary treatment for venomous snake bites, its various shortcomings have driven the development of safer and more effective alternatives. The use of heterologous immunoglobulins derived from animals poses a high risk of immunological reactions, which is a major concern (Dias da Silva et al. 2022). Therefore, new-generation antivenoms with lower immunogenicity have become the focus of much research.

The use of antibody fragments such as Fab and F(ab')₂, which have a smaller molecular size than intact immunoglobulins, is one of the approaches currently being extensively developed. It is hoped that these fragments will retain the ability to neutralize toxins while reducing the likelihood of

hypersensitivity reactions. Monoclonal and recombinant antibody technologies are also being developed as more specific alternatives targeting specific parts of the toxin (Dias da Silva et al. 2022).

Biotechnology also makes it possible to identify the toxin components that play the most significant role in the pathogenesis of envenomation. This allows for the development of more targeted therapies. It is projected that these molecular-based methods will improve therapeutic efficacy and expand the scope of protection against various venomous snake species (Guidolin et al., 2023).

Research has led to the use of adjuvant therapies, which can reduce tissue damage and excessive inflammatory responses, in addition to the development of antivenoms. One strategy currently being investigated to support the effectiveness of envenomation therapy is the use of antioxidants, metalloproteinase inhibitors, and anti-inflammatory agents (Alsolaiss et al., 2022).

Based on the findings from various studies that have been analyzed, it is clear that envenomation is a complex process in which the toxic effects of snakes and the body's immune response interact with one another. Snakes possess numerous substances known to activate the complement system, stimulate the release of pro-inflammatory cytokines, and damage tissues, leading to local and systemic clinical symptoms (Gabrili et al., 2022). Antivenoms, on the other hand, remain the primary treatment for removing toxins, but their use can also trigger immune reactions such as hypersensitivity and serum sickness (Dias da Silva et al., 2022). These findings indicate that the success of venomous snake bite therapy depends on both the antivenom's ability to neutralize toxins and the management of the associated immune response. Therefore, to improve patient clinical outcomes, both toxicological and immunological components must be considered when developing safer and more effective therapies.

Clinical Relevance

This study indicates that the management of venomous snake bites must take into account not only toxin neutralization but also the immune response during the envenomation process and following antivenom administration. Understanding immunological mechanisms is crucial for healthcare professionals to identify complications and provide appropriate treatment. In clinical practice, antivenom administration must be performed under close monitoring to prevent acute hypersensitivity reactions. Healthcare facilities providing antivenom therapy must be prepared to manage anaphylaxis, which includes having epinephrine, antihistamines, corticosteroids, and adequate resuscitation equipment on hand (Feng et al., 2022)

In addition, it is important to identify symptoms of serum sickness promptly, as reactions may appear several days after the patient is discharged. In cases of immunological complications, earlier intervention can be achieved by informing patients of the symptoms to watch for (Pineda & Ra, 2025)

This study is also relevant for health policy-making, particularly in countries with high rates of snakebites. Reducing mortality and disability caused

by venomous snakebites is greatly aided by improved access to high-quality antivenom, training for healthcare workers, and strengthening referral systems.

Limitations of the Study

When interpreting the research findings, several limitations should be noted. First, the articles used in this study were drawn from various types of research, each with different designs, populations, and methods, so the results may vary significantly. Second, most of the studies analyzed were conducted in specific locations involving various snake species. Clinical manifestations, immune responses, and antivenom efficacy may be influenced by differences in venom composition across species. Therefore, the study results cannot always be generalized to all snake bite cases (Simangunsong et al., 2024). Third, few studies specifically address the relationship between snake venom toxicity and the immune response to antivenom. Most studies focus on the clinical aspects of envenomation or the efficacy of antivenom, so further research is needed to understand the immunological mechanisms.

Fourth, this study is a literature review, so its findings depend on the quality and completeness of the data from the publications analyzed. Therefore, further experimental and clinical research is needed to support the evidence regarding how snakes, antivenoms, and the immune system interact with one another.

CONCLUSIONS AND RECOMMENDATION

Snake venom is a highly complex mixture of various bioactive proteins, peptides, and enzymes that have direct toxic effects and influence the immune system. Various pathophysiological mechanisms occur during the envenomation process, including activation of the complement system, release of proinflammatory cytokines, oxidative stress, and endothelial dysfunction. All of these lead to inflammation, tissue damage, coagulation disorders, and a number of systemic complications. The type of snake, the composition of the venom, the amount of toxin entering the body, and the physical condition of the person bitten influence the intensity of the response.

Antivenom remains the primary and most effective specific therapy for neutralizing snake venom and reducing morbidity and mortality resulting from envenomation. However, since most antivenoms are still derived from heterologous immunoglobulins sourced from animals, their use carries a potential risk of early hypersensitivity, anaphylaxis, and serum sickness resulting from the formation of immune complexes. Therefore, antivenom administration must be accompanied by close monitoring to identify and manage potential adverse reactions promptly and appropriately.

The use of antibody fragments, monoclonal antibodies, and improved protein purification techniques has enabled the development of a new generation of antivenoms that are safer and more effective. It is hoped that these innovations will enhance toxin neutralization capabilities while reducing the likelihood of immunological reactions. Therefore, understanding how venom interacts with antivenoms and the immune system is crucial for developing better, safer, and higher-quality therapeutic methods to treat patients bitten by venomous snakes.

FURTHER STUDY

This study still has limitations because most of the literature used comes from research with various designs, methods, and research subjects. In addition, studies that specifically address the relationship between snake venom toxicity, immune response, and immune reactions to antivenom are still very limited.

Therefore, future research should focus on experimental and clinical studies to gain a better understanding of how snake venom, antivenom, and the immune system interact with one another. Furthermore, ongoing research is needed to develop a new generation of antivenoms that are safer and do not pose a higher risk of immunological reactions, thereby improving treatment efficacy in patients bitten by venomous snakes.

ACKNOWLEDGMENT

The author would like to thank the academic community of the Faculty of Pharmacy at Jenderal Achmad Yani University for their advice, feedback, and support throughout the writing of this article.

REFERENCES

- Ahmad, B., & Rehatta, N. M. (2024). Naja kaouthia snake bite: Case report. *JAI (Jurnal Anestesiologi Indonesia)*, 16(3), 249–255. <https://doi.org/10.14710/jai.v0i0.59758>
- Alsolaiss, J., Evans, C. A., Oluoch, G. O., Carter, N. R., & Harrison, R. A. (2022). Profiling the murine acute phase and inflammatory responses to African snake venom: An approach to inform acute snakebite pathology. *Toxins*, 14(4), 229. <https://doi.org/10.3390/toxins14040229>
- Charuwan, S., Rittilert, P., Vasaruchapong, T., Srisuma, S., Wananukul, W., & Trakulsrichai, S. (2022). Early adverse reactions to snake antivenom: Poison center data analysis. *Toxins*, 14(10), 694. <https://doi.org/10.3390/toxins14100694>.
- Simangunsong, D. K., Habib, H., & Simbolon, E. (2024). Pemberian SABU (serum anti-bisa ular) pada kasus gigitan ular dengan komplikasi DIC. *Cermin Dunia Kedokteran*, 50(2), 149–155.
- Dias, J. A., & Vasconcelos, R. M. (2023). Acidentes por animais ofídicos: repercussões sistêmicas e prognóstico. *Brazilian Journal of Health Review*, 6, 12520–12531. <https://doi.org/10.34119/bjhrv6n3-321>
- Dias da Silva, W., Tambourgi, D. V., & Santoro, M. L. (2022). Antibodies as snakebite antivenoms: Past and future. *Toxins*, 14(9), 606. <https://doi.org/10.3390/toxins14090606>

- Feng, J., Wu, Z., Yu, Q., Li, H., Ji, P., Yang, Y., Wang, X., Zhang, L., Chen, Y., Liu, S., & Zhao, H. (2022). Hydrocortisone for preventing adverse drug reactions to snake antivenom: A meta-analysis. *Evidence-Based Complementary and Alternative Medicine*, 2022, 6151206. <https://doi.org/10.1155/2022/6151206>
- Gabrili, J. J. M., Squaiella-Baptistão, C. C., Leonel, T. B., Tambourgi, D. V., Oliveira, C. F., & Silva, M. R. (2023). New insights into immunopathology associated with *Bothrops lanceolatus* snake envenomation: Focus on PLA2 toxin. *International Journal of Molecular Sciences*, 24(12), 9931. <https://doi.org/10.3390/ijms24129931>
- Gabrili, J. J. M., Squaiella-Baptistão, C. C., Leonel, T. B., Tambourgi, D. V., Oliveira, C. F., & Silva, M. R. (2022). *Bothrops jararaca* snake venom inflammation induced in human whole blood: Role of the complement system. *Frontiers in Immunology*, 13, 885223. <https://doi.org/10.3389/fimmu.2022.885223>
- Guidolin, F. R., de Godoi, K. S., Megale, A. A. A., da Silva, C. C. F., Kodama, R. T., Cajado-Carvalho, D., Pereira, L. M., Silva, R. S., Almeida, J. R., & Oliveira, F. A. (2023). Comparing traditional and toxin-oriented approaches towards antivenom production against *Bitis arietans* snake venom. *Toxins*, 15(9), 584. <https://doi.org/10.3390/toxins15090584>
- Herrera-Vara, M., Ricaldi-Contreras, E., Santa-María-Huamani, E., Santiago-Esteban, M., & Panduro-Correa, V. (2026). Prophylactic antihistamines in adverse reactions to snake antivenom: A systematic review of randomized controlled trials. *Medical Information Center*. <https://doi.org/10.54034/mic.e2689>
- Negrin, A., Battocletti, M. A., Juanena, C., & Morais, V. (2021). Reports of doses administered and adverse reactions to snake antivenom used in Uruguay in 2018. *Frontiers in Toxicology*, 3, 690964. <https://doi.org/10.3389/ftox.2021.690964>
- Patel, R., Makwana, H. D., Sood, S., & Malhotra, S. (2021). A hypersensitivity following antivenom administration: A case report. *Journal of Pharmaceutical and Drug Research*. <https://doi.org/10.53411/jpadr.2021.2.4.6>
- Patel, D. C., Sovani, V. B., & Patel, N. J. (2024). Post marketing evaluation of anti snake venom (ASV) administered as a standard treatment for snakebite: Experience from western India. *Indian Journal of Public Health Research and Development*, 15(4), 279–285. <https://doi.org/10.37506/9w4gpf62>

- Pineda, D., & Ra, J. (2025). Case report purpura in serum sickness: A case of polyvalent snake antivenom reaction. *Revista de Patologia Tropical*, 54(2), 1–8. <https://doi.org/10.5216/rpt.v54i2.81822>
- Ryan, R. Y. M., Lutzky, V. P., Herzig, V., Smallwood, T. B., Potriquet, J., Wong, Y., & Fry, B. G. (2020). Venom of the red-bellied black snake *Pseudechis porphyriacus* shows immunosuppressive potential. *Toxins*, 12(11), 674. <https://doi.org/10.3390/toxins12110674>
- Khochare, S., Laxme, R. R. S., Jaikumar, P., Attarde, S., Kulkarni, A., Deshpande, A., & Sharma, R. (2023). Fangs in the Ghats: Preclinical insights into the medical importance of pit vipers from the Western Ghats. *International Journal of Molecular Sciences*, 24(11), 9516. <https://doi.org/10.3390/ijms24119516>
- Le, T. Q., Nguyen, N. T., Pham, Y. B., Tran, H. T., Nguyen, Q. L., & Le, H. T. (2025). Molecular mechanisms of efficacy variation in antivenoms: Insights from a Malayan pit viper bite in Vietnam. *Tropical Medicine and Infectious Disease*. <https://doi.org/10.3390/tropicalmed10120331>
- Simangunsong, D. K., Habib, H., & Simbolon, E. (2024). Pemberian SABU pada kasus gigitan ular dengan komplikasi DIC. *Cermin Dunia Kedokteran*, 51(3), 941. <https://doi.org/10.55175/cdk.v51i3.941>