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Ethnomedicinal breakthroughs in snake bite therapy: From folklore to forefront

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A B S T R A C T

Snakebite envenomation is a critical public health issue, especially in tropical regions like India, resulting in significant morbidity and mortality. This review explores the potential of ethnomedicinal herbs as adjunct therapies to conventional antivenoms, addressing challenges such as the high cost, limited availability, and side effects of traditional antivenoms. The study emphasizes regional and species-specific variations in snake venom that complicate antivenom development and highlights the pharmacological potential of certain medicinal plants in mitigating venom effects. These plants offer an affordable, accessible alternative, though their efficacy can vary due to regional venom differences. Additionally, the review discusses the role of bioinformatics in advancing antivenom research, aiming to combine traditional knowledge with modern science to develop effective and accessible snakebite treatments in resource-limited settings.

1. Introduction

In India, a country characterized by a diversified terrain adorned with bright colors, there exists a stealthy predator - the poisonous snake [1]. Snakebite envenomation affects approximately 5.4 million people globally each year, leading to 1.8–2.7 million envenomation cases and 81,410 to 137,880 deaths, with significant morbidity including amputations and lifelong impairments [2]. Research predominantly focuses on front-fanged venomous snakes due to their higher morbidity and mortality rates, whereas rear-fanged species remain understudied [3,4]. Certain biological products termed as antivenoms can be used as an effective treatment option against snake envenomation. The antivenoms act by inactivating the toxic components by neutralizing them. Kaur et al. [5–7]. The overall process of snake venom neutralization by plant phytocompounds is depicted in Fig. 1.

Conventional antivenoms are often limited by high production costs, narrow efficacy spectra, and distribution challenges, making them less accessible to those in rural and resource-limited settings [8-10].

Throughout history, communities have preserved the knowledge of plant-derived medicinal remedies that have been handed down from one generation to the next [11,12]. Ethnomedicinal plants have long been used in traditional snakebite treatments, offering potential as adjunctive therapies due to their ability to neutralize venom toxins, particularly in regions with limited access to conventional antivenoms [11-14].

Despite these promising avenues, significant challenges exist in integrating traditional remedies with modern therapeutic approaches. Issues like the standardization of plant extracts, comprehensive toxicity testing, and sustainable harvesting practices must be addressed to ensure the safe and effective use of ethnomedicinal plants. To transform this rich traditional knowledge into clinically viable solutions, systematic documentation and rigorous scientific validation are essential. This review aims to bridge the gap between traditional practices and contemporary scientific approaches, offering an integrated strategy for effective snakebite management. It ultimately seeks to provide new, accessible, and effective treatments, especially for those in resource-limited settings, by harnessing the therapeutic potential of India's diverse flora.

The novelty of this review lies in its comprehensive exploration of the potential for ethnomedicinal plants as adjunctive therapies to conventional antivenom treatments for snakebite envenomation, with a focus on the Indian context. This review contributes to the advancement of knowledge by integrating traditional ethnomedicine with modern

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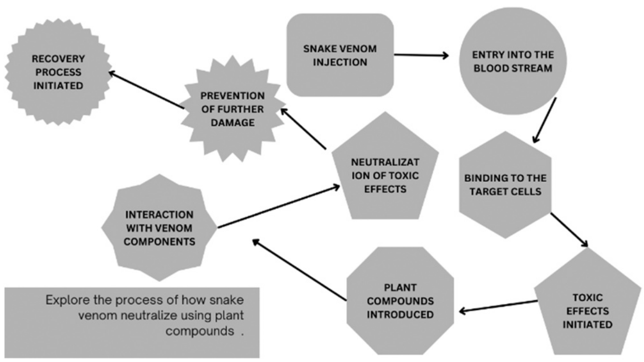

Fig. 1. The process of snake venom neutralization by plant phytocompounds.

scientific approaches, providing a dual perspective that highlights the regional specificity of venom compositions and the effectiveness of plant-based therapies. This review addresses the challenges faced by current antivenoms—such as limited accessibility, high costs, and a narrow spectrum of efficacy—while showcasing the potential of phytocompounds in neutralizing venom effects. Moreover, it discusses the role of bioinformatics and molecular docking techniques in accelerating the discovery of new antivenom strategies and suggests the incorporation of nanotechnology to enhance the delivery of traditional remedies.

2. Snake venom diversity and challenges in antivenom development

2.1. Snake venom composition and effects

India, a country known for its rich and varied biodiversity, is home to a wide range of poisonous snakes, which provide a considerable risk to human health. Gaining knowledge about the many species of these snakes and their venom compositions is essential to creating efficient antivenoms and effectively handling snakebite envenomation. India boasts over 270 snake species, of which approximately 60 are venomous. These snakes exhibit distinct geographical ranges and possess powerful venom compositions (Avni Gupta January 28, 2022). The Indian Cobra (*Naja naja*), prevalent across South Asia, possesses a venom rich in neurotoxins, cytotoxins, and cardiotoxins, posing a significant health risk [15]. Neurotoxins result in paralysis, cytotoxins lead to damage in the surrounding tissues, and cardiotoxins affect the circulatory system. These toxins combined constitute a substantial risk to human health [16,17].

The Common Krait (*Bungarus caeruleus*) is a well-known poisonous snake found in the region and in a member of the family Elapidae. It is often found in rural and agricultural parts of the Indian subcontinent, including India, Pakistan, Nepal, and Sri Lanka [9]. The venom of the Common Krait mostly consists of neurotoxins, which cause respiratory paralysis. In addition, presynaptic toxins impact the nerve cells, hence increasing the venomous strength of the snake [18].

The Russell's Viper *(Daboia russelii*) is found in a variety of environments, including grasslands and woodlands, primarily in South Asia and in the member of the family viperidae. Its range extends from India to Southeast Asia and southern China [15]. Russell's Viper venom is distinguished by a blend of hemotoxic and cytotoxic elements, resulting in both localized tissue harm and systemic consequences, such as coagulopathy and bleeding [19].

Saw-scaled Vipers (*Echis carinatus*) from the Viperidae family are well-suited to the many terrains of the Indian subcontinent, including deserts, grasslands, and rocky places. They can be found across the Indian subcontinent, the Middle East, and some regions of Africa [9]. The venom of Saw-scaled Vipers is characterized by the presence of hemotoxic and cytotoxic components, which have strong effects on blood coagulation and cause damage to local tissues [19].

The wide range of venom compositions presents significant obstacles in the development of antivenoms [20]. Antivenoms with broad effectiveness often have limited efficacy against specific venoms, emphasizing the need for region-specific antivenoms specific to the snake populations in local areas [8]. Moreover, the high costs and limited accessibility of antivenoms in rural regions create additional challenges. Nevertheless, the extensive diversity of venom also offers opportunities for research and advancement [21]. Analyzing venom components can lead to the identification of innovative therapeutic compounds that may have potential applications in pain management, cancer treatment, and other medical fields [22]. Furthermore, investigating the mechanisms by which certain animals are resistant to venom could contribute to the development of safer and more efficient antivenoms [23]. ,

2.2. Venom composition variability in Indian snakes

India, a country known for its rich and diverse wildlife, is home to a fascinating and potentially dangerous reptile population - poisonous snakes. Although these captivating organisms fulfill important ecological functions, their powerful toxins provide a substantial risk to public health, resulting in the loss of thousands of lives each year. Understanding the complex structure of venom composition in Indian snakes is crucial for both treating envenomation effectively and gaining knowledge about the interplay between evolutionary forces and interactions with prey. This comprehensive investigation examines the several complex elements that affect the composition of venom, specifically emphasizing the impact of nutrition, regional differences, and variations within species. Each of these aspects is supported by a rich array of relevant sources.

2.2.1. Factors influencing venom composition

The composition of snake venom is intricately linked to the diet and geographical variation of the species, reflecting a complex interplay between evolutionary adaptation and environmental factors. Research on Russell's viper (*Daboia russelii*) demonstrates how dietary preferences, such as frogs versus mammals, influence venom composition, leading to an increase in neurotoxins or hemotoxins respectively, to better target the biochemical defenses of their prey [24]. Similarly, cobras (Naja spp.) tailor their venom, rich in neurotoxins, to effectively immobilize their preferred reptilian and amphibian prey [25].

Geographical diversity further complicates venom composition, with snakes in different regions developing distinct venom profiles in response to local climate, habitat conditions, and prey availability. For instance, spectacled cobras (*Naja naja*) from hotter, drier areas possess higher levels of neurotoxins compared to those from cooler, wetter regions, suggesting an adaptation to the prey's habitat preferences [26]. The venom of kraits (Bungarus spp.) varies based on their interaction with diverse prey communities, adapting to capture resistant or varied prey effectively [27]. Additionally, genetic drift and local adaptation contribute to the regional differences in venom composition, as seen in the saw-scaled viper (*Echis carinatus*), which displays significant variability across its range in India [28]. These findings underscore the dynamic nature of venom composition, shaped by the diet, geographic location, and evolutionary pressures, highlighting the need for a nuanced understanding of venom variability in the context of snake ecology and evolution.

2.2.2. Intraspecific variability within species

When we examine the venom composition of a single species, the tale becomes much more complex. The variables other than location influence the composition of venom:

Gender Disparities: Certain Indian snakes have a notable variation in venom composition between males and females. Sexual dimorphism frequently arises from variations in prey choices or reproductive strategy. Research on the common krait (*Bungarus caeruleus*) indicates that male kraits have venom that is specifically adapted for hunting other snakes, whilst female kraits have a wider range of poisons that are suitable for a varied diet [29]. Comprehending these gender-specific differences is essential for customizing antivenom therapy and precisely determining the responsible snake in bite incidents.

Age-related Changes: As snakes progress through their life cycle, the composition of their venom transforms. Young individuals frequently have a deficiency in certain poisons or display distinct ratios of venom constituents in comparison to mature individuals. This phenomenon illustrates the changing nutritional requirements and susceptibility of individuals at various life stages. Young Russell's vipers, in contrast to adult ones, generally do not possess the powerful hemotoxin that is distinctive of the species. This difference may result in a decreased level of danger posed to humans by the young vipers [25,30]. Understanding these age-related differences is extremely important for evaluating risk and developing therapeutic approaches in cases of snakebites in children.

3. Mechanistic insights and therapeutic advances in snakebite envenomation treatment

The considerable diversity in venom composition presents difficulties for snakebite treatment. Antivenoms are usually developed to target venoms from specific geographic areas or individual species, which may result in their ineffectiveness against snake attacks with varying venom compositions [31]. This discrepancy adds to the ineffectiveness of treatments and emphasizes the necessity for: Researchers are now engaged in the development of antivenoms that are tailored to specific regions and can effectively neutralize a wider array of venom variants. This is being achieved using advanced purification techniques and the incorporation of venoms from varied populations [32]. Biomarker-based venom identification enables the rapid determination of the snake species and venom composition implicated in a bite, hence facilitating tailored therapy with appropriate antivenoms. Improved comprehension of the process of venom evolution: Further investigation into the determinants of venom variability is essential for enhancing the effectiveness of antivenom and formulating preventative measures [33, 34].

3.1. Comparative analysis of ethnomedicinal plants and conventional treatments for snake venom

Using ethnomedicinal plants for snake venom therapy provides a supplementary method to traditional antivenom treatments. So many advantages and possibilities of using ethnomedicinal herbs for the treatment of snake venom events Figs. 2–4.

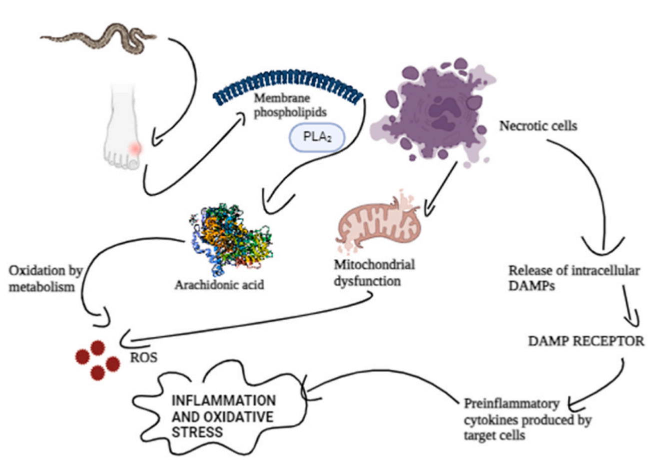

Fig. 2. Necrotic activity of venom components causing oxidative and inflammatory stress response: Mechanism of PLA2.

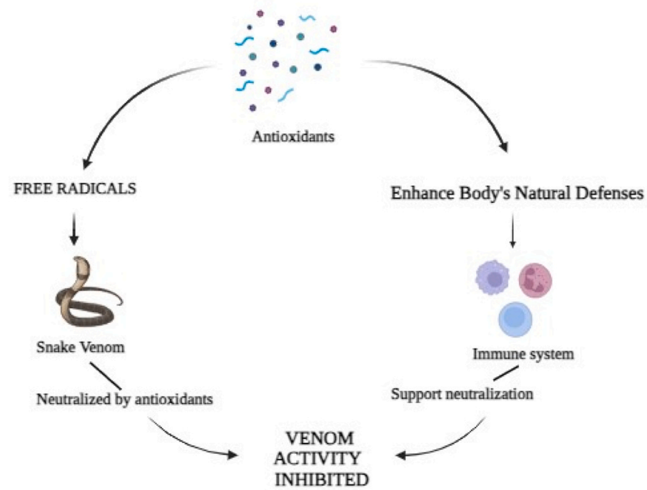

Fig. 3. Antioxidant activity inhibits snake venom.

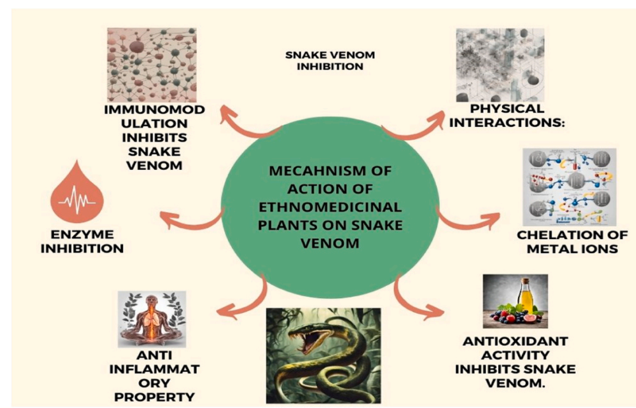

Fig. 4. Mechanisms of action of ethnomedicinal plants against snake venom.

3.1.1. Enhancing accessibility and ensuring cost-effectiveness

Ethnomedicinal herbs are often more accessible and cost-effective than conventional antivenoms, as observed in studies from East African and Indian communities [35]. The research shows that people in this society heavily depend on medicinal plants since they are easily accessible and have been traditionally used in rural places [36].

3.1.2. Pharmacological effectiveness

The pharmacological effectiveness of ethnomedicinal herbs against snake venom is extensively demonstrated. A research article published in the Journal of Pharmacognosy and Phytochemistry emphasizes the significance of phytochemical substances derived from ethnomedicinal plants in suppressing the activity of phospholipase A2, an enzyme commonly found in snake venoms [37]. Experimental research conducted on albino rats have demonstrated that some medicinal plants can successfully counteract snake venom. This finding serves as a scientific justification for the traditional use of these plants [38].

3.1.3. Potential for therapeutic applications

Ethnomedicinal herbs have demonstrated potential in healing the specific tissue damage resulting from snake bites, in addition to their ability to neutralize venom. Evidence-based Complementary and Alternative Medicine offers a comprehensive examination of plants that possess the ability to neutralize venom and promote the repair of tissue damage. This suggests that these plants have a diverse therapeutic potential that goes beyond what traditional antivenoms can deliver [39]. While conventional antivenom treatments remain the standard for snakebite management, ethnomedicinal plants offer a viable, complementary approach. Their accessibility, cost-effectiveness, and broad pharmacological activities make them an invaluable resource, particularly in under-resourced regions. Further research and integration into health systems could enhance the global response to snakebites Table 1.

4. Limitations of ethnomedicinal plants as antivenom against snakebite

The research on ethnomedicinal herbs as antivenoms for snake bites, while showing potential, is impeded by many constraints that impede its advancement and implementation. A major constraint is the lack of scientific research that confirms the effectiveness of plant-based treatments, especially in areas such as Central America where traditional use is common but not well studied [40]. Moreover, the intricate composition of snake venom and its wide-ranging impact on the body provide difficulties in creating a universally potent antivenom derived from plants. The variability of venom composition across various snake species adds to the complexity, making it challenging to create a universal plant-based remedy [41,42]. Another crucial concern is the possibility of negative consequences. Certain plant extracts, while they can suppress venom, may also have procoagulant or anti-thrombin properties that might worsen venom-induced coagulopathy [43]. The limited scope and strict storage requirements of existing antivenoms restrict their use, prompting the exploration of new therapies. Nevertheless, the literature still lacks a thorough examination of the phytochemical composition and safety assessments of these herbal treatments, which is a notable deficiency [44,45]. Furthermore, the use of traditional knowledge without empirical confirmation and the lack of regulated extraction procedures and doses make the creation of plant-based antivenoms more challenging [46,47]. The need for regional cooperation in addressing these difficulties is clear, as is the requirement for a strong and customized pharmaceutical research and development process for snakebite envenomation therapies [48,49]. To fully utilize the potential of ethnomedicinal plants in developing antivenoms, it is crucial to address the current studies. These limitations include the lack of scientific validation, the complexity of venom effects, potential adverse reactions, and the absence of standardized methodologies.

Table 1
Comparative Advantages of Ethnomedicinal Plants vs. Standard Treatments in Snake Venom Management.

Benefit	Ethnomedicinal Plants	Standard Treatments	References
Accessibility	Widely accessible, especially in remote areas where conventional treatments might not be available.	Limited accessibility, particularly in remote or under-resourced areas	[35], [36]
Cost	Generally cost-effective due to local availability and traditional knowledge.	Can be expensive and less affordable for many communities.	[35], [36]
Pharmacological Efficacy	Contains phytochemical compounds effective against various venom activities, including enzyme inhibition.	Primarily focused on neutralizing venom through specific antivenoms.	[37]
Therapeutic Potential	Offers broad therapeutic benefits, including tissue healing and reducing inflammation, beyond just neutralizing venom.	Mainly provides venom neutralization without additional healing properties	[38,39]
Cultural Acceptance	Deeply integrated into traditional healthcare practices, ensuring higher community trust and utilization	May face resistance or lack of trust in communities with strong traditional medicine practices.	[36], ` [39]

5. Phytocompounds as antivenom agents

Snake venoms, a complex mixture of proteins and enzymes, exert a diverse array of toxic effects, including neurotoxicity, myotoxicity, coagulopathy, and cytotoxicity. These effects are largely attributed to the enzymatic activities of venom components, such as phospholipase A2 (PLA2), hyaluronidases, proteases, and metalloproteinases. The development of effective antivenom therapies remains a significant challenge, necessitating the exploration of alternative strategies. Phytocompounds, derived from medicinal plants, have emerged as promising candidates for the management of snakebite envenomation. These natural products exhibit a wide range of pharmacological activities, including antioxidant, anti-inflammatory, and anti-venom properties. By targeting specific venom components, phytocompounds can mitigate the deleterious effects of envenomation.

A significant body of research has focused on the inhibition of PLA2 by phytochemicals. This enzyme plays a pivotal role in venom-induced tissue damage, inflammation, and hemolysis. Various plant species, including *Vitex negundo*, *Indigofera pulchra*, *Aristolochia albida*, and *Andrographis paniculata*, have been reported to contain compounds with potent PLA2 inhibitory activity [37,50,51]. For instance, flavonoids, such as rutin and gallocatechin, have been identified as potent PLA2 inhibitors, suggesting their potential as therapeutic agents [50].

Beyond PLA2 inhibition, phytocompounds exhibit other mechanisms of action against snake venom. Antioxidant properties of compounds like those found in Andrographis paniculata can mitigate oxidative stress, a common consequence of snakebite envenomation [52]. Additionally, phytochemicals can modulate inflammatory responses, reducing tissue damage and edema.

The integration of traditional knowledge with modern scientific techniques has facilitated the discovery and characterization of phytocompounds with antivenom properties. In-silico studies, such as molecular docking, have provided valuable insights into the binding interactions between phytochemicals and venom components, aiding in the identification of potential lead compounds [52].

While phytocompounds offer promising therapeutic potential, several challenges remain. Standardization of plant extracts, identification of bioactive compounds, and preclinical and clinical evaluation are essential steps toward developing effective phytocompound-based antivenom therapies. Moreover, the complex nature of snake venoms necessitates the exploration of combination therapies involving multiple phytocompounds to address the diverse effects of envenomation. Phytocompounds represent a rich source of potential antivenom agents. By targeting key venom components and exerting multiple pharmacological actions, these natural products offer a promising avenue for the development of novel and effective treatments for snakebite envenomation Table 2.

6. Mechanisms of action of ethnomedicinal plants against snake venom

Ethnomedicinal plants target venom enzymes like phospholipases, hyaluronidases, and proteases, reducing the venom's toxicity through inhibitory effects.

6.1. Enzyme inhibition

Enzyme inhibition occurs when certain compounds found in ethnomedicinal plants directly hinder the enzymatic function of snake venom components. Specific phytochemicals can inhibit phospholipases A_2 (PLA_2s) by blocking their active sites, therefore limiting the hydrolysis of phospholipids in cell membranes, which is crucial in venom-induced cytotoxicity [37].

Table 2
List of phytocompounds with inhibitory activity against .snake venom proteins.

Sl. No.	Phytocompounds	Snake Venom Protein	Activity of Inhibition	References
1	*Mandevilla velutina* extract	Phospholipase A2 (PLA2)	Inhibits phospholipase, myotoxic, and hemorrhagic activities	[53]
2	*Withania somnifera* glycoprotein (WSG)	Hyaluronidase	Inhibits hyaluronidase activity	[54]
3	PEGylated gold nanoparticles	NKCT1 peptide (*Naja kaouthia*)	Inhibits anticancer activity, reduces toxicity	[55]
4	Various plant extracts	Bitanarin (Phospholipase A2)	Inhibits nicotinic acetylcholine receptors	[56]
5	Saxatilin (*Gloydius saxatilis*)	-	Inhibits platelet aggregation, endothelial cell proliferation	[57]
6	Triacontyl p-coumarate	Snake venom metalloproteinases	Inhibits fibrinogenolytic, hemorrhagic, and myotoxic activities	[58]
7	*Andrographis paniculata* (MAP) extract	Acetylcholinesterase, Hyaluronidase	Inhibits neurotoxic enzyme acetylcholinesterase and hyaluronidase	[59]
8	Erythroxylum spp. extracts	Lachesis muta venom	Inhibits hemorrhage, edema, proteolysis, coagulation, hemolysis	[60]
9	*Piper umbellatum* and *Piper peltatum*	Myotoxin I (Bothrops asper)	Inhibits the enzymatic activity of myotoxin I, reduces myotoxicity	[61]
10	*Andrographis paniculata* phytochemicals	Phospholipase A2 (PLA2)	Inhibits PLA2, reduces oxidative stress	[52]
11	γBjussuMIP (*Bothrops jararacussu*)	Phospholipase A2 (PLA2)	Inhibits phospholipase, anticoagulant, myotoxic, edema-inducing activities	Oliveira et al., 2009
12	*Elephantopus scaber* (crepiside E)	Phospholipase A2 (PLA2)	Inhibits catalytic activity of PLA2	[62]
13	Aristolochic alkaloid	Phospholipase A2 (PLA2)	Inhibits PLA2, reduces edema	[63]
14	Flavonoids and neoflavonoids	Phospholipase A2 (PLA2)	Inhibits PLA2, reduces edema	[63]
15	*Tragia involucrata* compounds	Phospholipase A2 (PLA2)	Inhibits PLA2, reduces edema	[63]
16	Manoalide and its derivatives	Phospholipase A2 (PLA2)	Inhibits PLA2	[63]
17	Scalaradial and related compounds	Phospholipase A2 (PLA2)	Inhibits PLA2	[63]
18	Pseudopterosins and vidalols	Phospholipase A2 (PLA2)	Inhibits PLA2	[63]
19	Tetracycline	Phospholipase A2 (PLA2)	Inhibits PLA2	[63]
20	Erythroxylum spp. compounds	Lachesis muta venom	Inhibits hemorrhage, edema, proteolysis, coagulation, hemolysis	[60]

Kankara, Abdullahi, and Paulina [37] emphasize the effectiveness of plant extracts and isolates in deactivating venom enzymes, suggesting a possible path for innovative pharmacological advancements. This change in focus towards plant medicines supports sustainable medication discovery and preserves traditional knowledge, providing both effectiveness and availability. Research in Central America has highlighted the potential of plants like *Eryngium foetidum* L., *Neurolaena lobata*, and *Pimenta dioica* in reducing the enzymatic activity associated with the venom of *Bothrops asper*. Saravia-Otten *et al.,* [64] found that secondary metabolites from these plants strongly interact with the venom's metalloproteinases and PLA_2s, indicating their ability to suppress the venom's harmful components using molecular docking studies.

Studies have explored how extracts from *Renealmia alpinia* can inhibit venomous enzymes from *Bothrops atrox* and *Crotalus durissus cumanensis*. The research indicates that secondary metabolites from the plant interact with snake venom proteinases in a non-proteolytic manner [65]. This method of action, apart from proteolytic breakdown or protein clumping, emphasizes the subtle ways in which plant chemicals might counteract venom toxicity. Research conducted by Molander et al., [66] in Mali, DR Congo, and South Africa revealed the effectiveness of traditional botanicals in stopping snakebite-induced tissue necrosis. These plants can help reduce the effects of snake venom by blocking important enzymes such as hyaluronidase, PLA_2s, and proteases. They are a valuable resource for treating envenomation, especially in areas like sub-Saharan Africa where traditional medical care may not be easily accessible. These findings confirm the medical benefits of ethnomedicinal herbs and suggest combining traditional healing knowledge with current treatment approaches to treat snakebites.

6.2. Chelation of metal ions

Some snake venom enzymes, particularly metalloproteases, require metal ions like Zn^{2+} for their activity. Certain compounds found in ethnomedicinal plants can chelate these metal ions, rendering the enzymes inactive. This inhibits the venom's ability to cause local tissue damage and necrosis.

A snake venom study has revealed an interesting interaction between natural inhibitors and venom metalloproteases, suggesting possible therapeutic paths including ethnomedicinal chemical compounds from plants. A significant research study on *Bothrops jararaca* venom discovered that citrate, a natural element found in the venom, acts as an inhibitor of self-proteolysis by binding to calcium ions that are essential for metalloprotease activity [67]. This finding suggests interesting similarities with phytochemicals found in traditional therapeutic plants, which may use comparable chelating methods to counteract the harmful effects of venom. Additionally, a study on *Baccharis trimera* found a neo-clerodane diterpenoid that may completely prevent venom-induced hemorrhage and proteolysis, likely by chelating metal ions [68]. This research highlights the potential of plant-based compounds, such as triacontyl p-coumarate from *Bombacopsis glabra*, in reducing venom effects by interacting with metalloproteinases, presumably through chelation processes [58].

Research has shown that chelating agents like $CaNa_2EDTA$ and inhibitors such as batimastat are effective in counteracting the tissue damage caused by *Bothrops asper* venom. This emphasises the importance of metal ion chelation in inhibiting venom effects [69]. Extracts from *Renealmia alpinia*, historically used for snakebites, have shown inhibitory effects on venom metalloproteinases and serine proteinases, suggesting chelation as a possible mechanism [65]. The results confirm the potential of ethnomedicinal plants in healing snake bites and suggest using compounds derived from plants with chelating properties for developing new antivenom techniques.

6.3. Physical interactions

The burgeoning field of ethnomedicine has unveiled promising strategies in combating snake venom toxicity, notably through the physical interactions between plant-derived compounds and venom molecules. This novel approach, focusing on obstructing the venom's ability to bind to human cell receptors, offers a pathway to neutralize venom without altering its enzymatic functionality. A pivotal study by Saravia-Otten et al. [41] on Central American ethnomedicinal plants, such as *Eryngium foetidum* L., *Neurolaena lobata*, and *Pimenta dioica*, revealed that their secondary metabolites could inhibit *Bothrops asper* venom by potentially blocking venom components through high-affinity interactions. This suggests a direct physical impediment of the venom's toxic actions by plant compounds.

Further supporting this concept, research by Kankara, Abdullahi, and Paulina [37] identified phytochemicals like betulinic acid, luteolin, and kaempferol with pronounced inhibitory effects on snake venom PLA_2

enzymes, likely through physical interference that neutralizes toxicity. Additionally, studies such as those by Otero et al. [70] in Colombia have demonstrated the ability of plants like *Brownea rosademonte* and *Tabebuia rosea* to completely neutralize hemorrhagic effects of *Bothrops asper* venom, hinting at the physical blockade of venom-induced hemorrhage by plant constituents. These findings, coupled with the insights from Mors, Nascimento, Pereira, and Pereira (2000), who proposed that plant-derived micromolecules could mimic the venom-neutralizing actions of endogenous macromolecules, underscore the therapeutic potential of ethnomedicinal plants. By physically interacting with venom molecules to prevent their binding to cellular targets, these plants offer a rich reservoir for developing innovative, non-enzymatic antivenom therapies.

6.4. Antioxidant activity inhibits snake venom

The exploration of ethnomedicinal plants as a countermeasure against the oxidative stress induced by snake venom represents a promising avenue in the development of adjunctive therapies for snakebite envenomation. The oxidative damage caused by snake venoms, particularly those from vipers, kraits, and cobras, involves the generation of free radicals, leading to cellular injury and inflammation. Research has increasingly focused on the antioxidant properties of plant-derived compounds, revealing their potential in neutralizing these venom-induced radicals and reducing oxidative stress.

A notable study by Kankara, Abdullahi, & Paulina [37] reviewed the inhibitory effects of various phytochemicals found in ethnomedicinal plants on snake venom phospholipase A_2 (PLA_2) enzymes, a key contributor to venom toxicity. Compounds such as luteolin, kaempferol, and ellagic acid, known for their potent antioxidant properties, were highlighted for their capacity to mitigate venom-induced oxidative damage. This aligns with the broader understanding, as discussed by Blokhina, Virolainen, & Fagerstedt [71], of antioxidants' crucial role in managing oxidative stress and inflammation, suggesting that plant-derived antioxidants can significantly influence the cellular redox state disrupted by venom.

Further reinforcing the therapeutic potential of plant antioxidants, Kasote, Katyare, Hegde, & Bae [72] delved into the application of these natural compounds in treating diseases associated with oxidative stress, underscoring their value in enhancing the body's defense mechanisms against the deleterious effects of snake venom. Ethnobotanical surveys, such as those conducted in Southern Tamilnadu and Koraput, Odisha, have documented the traditional use of plants like *Aristolochia indica, Hemidesmus indicus, Rauvolfia serpentina,* and *Mimosa pudica,* which possess significant antioxidant activity, offering protective effects against venom-induced oxidative stress [73,74].

These findings collectively highlight the potential of ethnomedicinal plants and their antioxidant components in providing a complementary approach to managing snakebite envenomations. The ability of these plants to neutralize venom-induced radicals and ameliorate oxidative damage opens new pathways for therapeutic intervention, warranting further research and clinical validation to fully harness their benefits in snakebite treatment.

6.5. Immunomodulation inhibits snake venom

The exploration of ethnomedicinal plants for their immunomodulatory properties against snake venom has opened new avenues in the development of complementary therapies for snakebite management. These plants, traditionally used in various cultures for treating snakebites, have been scientifically validated for their ability to neutralize venom-induced toxicities, such as lethality, hemorrhage, and inflammation, through modulation of the immune response. The methanolic root extracts of *Vitex negundo* and *Emblica officinalis*, for instance, have demonstrated significant neutralizing effects against the venoms of *Vipera russellii* and *Naja kaouthia*, underscoring the potential of these plants in enhancing the body's defense mechanisms against venom [75].

A comprehensive review by Soares et al. [76] correlated ethnopharmacological practices with empirical data, revealing a wide array of plant extracts that inhibit the principal toxic effects of snake venoms, hinting at underlying immunomodulatory mechanisms. Similarly, studies on *Jatropha gossypiifolia* and *Mangifera indica* have shown these plants' extracts to significantly inhibit the enzymatic and pharmacological actions of *Bothrops jararaca* and *Daboia russellii* venoms, respectively. These findings suggest that the extracts may modulate the immune system to neutralize venom components, thereby mitigating edema, hemorrhage, and myotoxicity [77,78].

Moreover, research on Erythroxylum species, specifically *Erythroxylum ovalifolium* and *Erythroxylum subsessile*, has revealed their efficacy in neutralizing the venom-induced hemorrhage of *Lachesis muta*, further supporting the role of plant extracts in immune modulation [60]. These studies collectively highlight the immunomodulatory potential of ethnomedicinal plants in snakebite treatment, providing a scientific basis for their traditional use and suggesting a promising strategy for enhancing the body's natural defense against snake venom. Further investigation is warranted to elucidate the precise mechanisms through which these plant extracts exert their effects and to assess their potential in clinical applications for snakebite therapy.

7. Bioinformatics: a catalyst in ethnomedicinal antivenom research

The identification of effective antivenom agents remains a critical challenge in the management of snakebite envenomation. In recent years, bioinformatics accelerates the discovery of plant-derived inhibitors by analyzing interactions between phytocompounds and venom toxins. Structural bioinformatics, as exemplified by Prabasari *et al.* (2023), has been instrumental in predicting the three-dimensional structure of venom toxins and identifying potential binding sites for bioactive compounds. A case in point is the study by Sani et al. [38], which employed bioinformatics to screen plant extracts for antivenom potential against a panel of snake venoms, leading to the identification of *Bauhinia rufescens* seed extract as a promising candidate. Furthermore, the integration of bioinformatics with experimental studies has streamlined the drug discovery pipeline by enabling the prioritization of promising compounds for further evaluation [79,80].

Molecular docking and simulation techniques have proven invaluable in understanding the molecular mechanisms underlying the inhibitory effects of phytochemicals on snake venom toxins. Alshammari et al. [81] and Luzuriaga-Quichimbo *et al.* (2019) demonstrated the utility of these computational methods in identifying potential antiophidic compounds and elucidating their binding modes to venom targets. Notably, phospholipase A2 (PLA2) has been a focal point of antivenom research, with studies by Kankara et al. [37] and Singh et al. (2019) highlighting the potential of plant-derived compounds as PLA2 inhibitors. The growing body of evidence underscores the potential of ethnomedicinal plants as a rich source of antivenom candidates. However, further bioinformatics-driven research is imperative to fully exploit this resource. As advocated by Adrião et al. [82] and Dhanya et al. [83], increased investment in bioinformatics research is essential to translate traditional knowledge into effective therapies for snakebite envenomation. The discovery and development of novel antivenom agents often involve the isolation and synthesis of plant-derived secondary metabolites. Bioinformatics plays a crucial role in this process by facilitating structure-based drug design and optimization. By combining the power of bioinformatics with traditional ethnomedicinal wisdom, researchers can expedite the development of novel antivenom agents and ultimately improve the outcomes for snakebite victims.

8. New Therapeutic Strategies for Snakebite Management

8.1. Nanotechnology-Enhanced Antivenom Delivery

Nanotechnology offers a promising avenue for revolutionizing antivenom therapy by addressing the limitations of conventional antivenoms. By encapsulating antivenom antibodies or peptides within nanomaterials, researchers can significantly enhance their stability, bioavailability, and targeted delivery to the site of envenomation.

Key advantages of nanotechnology-based antivenom delivery:

•Enhanced stability: Nanoparticles protect antivenom components from degradation, extending their shelf life and improving their efficacy in neutralizing venom toxins.

•Increased bioavailability: Nanoparticles can facilitate the delivery of antivenom across biological barriers, improving drug absorption and distribution to the affected tissues.

•Targeted delivery: By functionalizing nanoparticles with specific ligands, researchers can achieve targeted delivery of antivenom to the site of venom injection, enhancing therapeutic efficacy and minimizing systemic side effects.

•Reduced immunogenicity: Nanoparticle-based delivery systems have the potential to reduce the immunogenicity of antivenom, minimizing allergic reactions and anaphylactic shock.

•Controlled release: Nanoparticles can be designed to release antivenom in a controlled manner, optimizing therapeutic effects and reducing the risk of overdose or under dosage.

•Combination therapy: Nanoparticles can be used to co-deliver multiple therapeutic agents, such as antivenom, antibiotics, and analgesics, to address the complex pathophysiology of snakebite envenomation.

Recent studies have demonstrated the efficacy of gold and silica nanoparticles in delivering antivenom components, resulting in enhanced venom neutralization [84,85]. Additionally, liposomal delivery systems offer the possibility of controlled release of antivenom in response to specific biological cues [86].

8.2. CRISPR/Cas9 for venom resistance and antivenom production

The emergence of CRISPR/Cas9 gene editing technology has opened new avenues for developing innovative strategies to combat snakebite envenomation. By modifying the genetic makeup of animals, researchers can create novel approaches for antivenom production and develop animal models for studying venom effects.

Potential applications of CRISPR/Cas9 in snakebite management:

•Development of venom-resistant livestock: Creating animals with genetic resistance to snake venom can provide a sustainable and cost-effective source of polyclonal antivenom.

•Generation of humanized antibodies: CRISPR/Cas9 can be used to modify the genetic code of animals to produce humanized antibodies, reducing the risk of allergic reactions.

•Development of venom-resistant animal models: These models can be used to study the mechanisms of venom action, identify novel therapeutic targets, and evaluate the efficacy of new antivenom treatments.

•Gene therapy for snakebite victims: While still in its early stages, CRISPR/Cas9 has the potential to be used for gene therapy to treat the effects of snakebite envenomation.

Creating venom-resistant livestock could serve as a sustainable source of antivenom antibodies (Zhao *et al.,* 2020). Furthermore, venom-resistant animal models can facilitate the identification of novel therapeutic targets and the development of countermeasures.

8.3. Immunotherapy and monoclonal antibodies

Immunotherapy, particularly the use of monoclonal antibodies, represents a targeted approach to snakebite treatment. These highly specific antibodies can neutralize specific venom components, thereby mitigating the systemic effects of envenomation.

Advantages of monoclonal antibodies for snakebite treatment:

•High specificity: Monoclonal antibodies can be designed to target specific venom toxins, reducing the risk of off-target effects and improving therapeutic efficacy.

•Potent neutralization: These antibodies can effectively neutralize venom toxins, preventing their harmful effects on various organs and tissues.

•Rapid action: Monoclonal antibodies can be administered quickly, providing immediate protection against venom.

•Combination therapy: Monoclonal antibodies can be used in combination with other antivenom components or therapeutic agents to enhance treatment outcomes.

•Potential for prophylaxis: Monoclonal antibodies could be developed as prophylactic agents to prevent snakebite envenomation in high-risk populations.

Recent advancements in antibody engineering have led to the development of monoclonal antibodies with enhanced efficacy and reduced immunogenicity [10,87,88]. These developments hold promise for the creation of more effective and safer antivenom therapies.

9. Recent advances in snake venom research

Recent advancements in scientific methodologies have significantly enhanced our understanding of snake venoms, paving the way for novel therapeutic interventions. Proteomics, phylogenetics, and synthetic biology have emerged as pivotal tools in unraveling the complexities of venom composition, evolution, and potential applications.

Proteomics has revolutionized venom research by enabling the comprehensive characterization of venom proteomes. Advancements in mass spectrometry and bioinformatics have facilitated high-throughput venom-gland transcriptomics and genomics, providing unprecedented insights into the structural diversity, expression patterns, and functional interactions of toxin genes (Tan, C. H. 2022). This knowledge has been instrumental in identifying specific venom components as targets for phytocompound-based therapies. Phytocompounds, derived from medicinal plants, have demonstrated promising antivenom properties by inhibiting various venom toxins, and mitigating the severe symptoms of snakebite envenomation (SBEs) [82].

Phylogenetics has contributed significantly to our understanding of venom evolution, revealing the intricate relationship between venom composition and snake phylogeny. By employing multi-omic approaches and advanced technologies like CRISPR and mass spectrometry imaging, researchers have gained insights into the genomic, transcriptomic, and protein-level modifications driving venom diversification [89]. These evolutionary insights have facilitated the identification of venom components with potential therapeutic applications and guided the development of synthetic venom analogs for research and therapeutic purposes.

Synthetic biology offers a promising avenue for developing innovative antivenom therapies. While traditional antivenom production relies on the hyperimmunization of animals, which often results in hypersensitivity reactions and supply limitations, synthetic biology aims to create safer and more effective alternatives. By leveraging plant-derived compounds with anti-myotoxic, anti-hemorrhagic, and anti-inflammatory properties, researchers are exploring the development of synthetic antivenom candidates [42]. Moreover, the discovery of anticancer properties in certain snake venom toxins has expanded the therapeutic potential of venom components beyond snakebite treatment [90].

Despite these remarkable advancements, several challenges persist in snake venom research. Limited access to venom samples, non-standardized quantitative methods, and regulatory restrictions on wildlife use hinder research progress, particularly in regions with high snakebite prevalence. Collaborative efforts between researchers worldwide and increased research funding are essential to address these limitations and fully exploit the potential of snake venom research for developing effective therapeutic interventions.

The integration of proteomics, phylogenetics, and synthetic biology has significantly advanced our understanding of snake venoms and opened new avenues for developing innovative antivenom therapies. By addressing the existing challenges and fostering international collaboration, researchers can harness the full potential of snake venom research to improve human health and well-being.

10. Some under-explored plants

In the realm of ethnomedicine, a plethora of plants are reputed for their antivenom properties, yet only a fraction has undergone rigorous scientific scrutiny to validate these claims. Among the unexplored, *Pittosporum* species *Glycosmis* species and *Aristolochia* species stand out for their traditional use in neutralizing Russell's viper venom. This review paper aims to bridge the gap between folklore and pharmacological research by highlighting the importance of these plants and advocating for their scientific exploration. *Pittosporum* species plants are endemic to the Western Ghats of India and are traditionally utilized for their wide range of medicinal properties, from treating rheumatism to snakebites. Despite its prevalent use in folklore, scientific studies elucidating its mechanisms against snake venom are conspicuously absent. Given its rich phytochemical profile, including flavonoids and triterpenoids, which are known for their anti-inflammatory and analgesic properties, this plant presents a promising candidate for antivenom research [91,92]. *Glycosmis* species is widely used in traditional medicine across Southeast Asia for its therapeutic effects, including antipyretic and antidote properties against snake venom. The plant's phytochemical constituents, such as alkaloids and limonoids, may offer clues to its potential mechanisms of venom inhibition. However, the absence of targeted venom studies leaves a significant gap in our understanding of its efficacy against snakebites [93]. *Aristolochia* species is another ethnomedicinal species of plants used in various Asian cultures for its supposed detoxifying effects, including as an antidote to snake venom. The presence of aristolochic acids and other bioactive compounds in Aristolochia species has been associated with anti-inflammatory and analgesic effects, which could hypothetically counteract venom-induced pathologies [94]. Yet, without empirical evidence, the plant's true potential in antivenom therapy remains speculative. The Need for Scientific Validation While many plants have been scientifically validated for their antivenom properties, these three remain largely unexplored due to possible factors such as geographical constraints, lack of interdisciplinary research collaboration, or prioritization of more commonly used medicinal plants. The importance of investigating these plants lies not only in validating traditional knowledge but also in the potential discovery of novel bioactive compounds that could contribute to more effective, accessible antivenom therapies. Given the global burden of snakebite envenomation and the limitations of current antivenom treatments, including accessibility, affordability, and species-specific efficacy, exploring these plants scientifically could yield valuable insights. Future research initiatives must focus on ethnobotanically informed studies, bioassays, and pharmacological testing to elucidate the mechanisms through which these plants may neutralize snake venom, thereby contributing to the broader antivenom research field.

11. Case studies of ethnomedicinal plant efficacy on inhibiting snake venom

11.1. Successful integrations of traditional and modern treatments

The integration of proteomics, phylogenetics, and synthetic biology has significantly advanced our understanding of snake venoms and opened new avenues for developing innovative antivenom therapies. By addressing the existing challenges and fostering international collaboration, researchers can harness the full potential of snake venom research to improve human health and well-being.

The integration of traditional ethnomedicine with contemporary scientific methodologies has shown immense promise in addressing the global burden of snakebite envenomation. Indigenous communities have relied on plant-based remedies for centuries, developing a rich repository of knowledge on species with potential antivenom properties.

Plants employed in traditional snakebite treatments often contain a diverse array of secondary metabolites, including flavonoids, alkaloids, and tannins. These compounds have demonstrated the ability to inhibit key venom enzymes, reduce inflammation, and counteract other systemic effects of envenomation [83]. For instance, *Vitex negundo*, a plant traditionally used in India, has been shown to neutralize the lethal effects of *V. russelli* and *Naja naja* venoms through its potent anti-inflammatory properties [51].

The synergy between ethnobotanical knowledge and modern scientific research has led to the identification of numerous plant species with antivenom potential. Studies conducted in Benin, India, Nigeria, Central America, and Tanzania have revealed a rich tapestry of medicinal plants traditionally used for snakebite treatment [45,64,95-98]. Phytochemical analysis of these plants has confirmed the presence of bioactive compounds, supporting their traditional use in snakebite management.

While traditional knowledge provides a valuable foundation, rigorous scientific investigation is crucial to validate the efficacy and safety of plant-based antivenom therapies. Preclinical studies have demonstrated the potential of many plant extracts in neutralizing venom components and mitigating envenomation symptoms. However, the translation of these findings into clinical practice requires well-designed clinical trials to assess their safety and efficacy in humans.

The successful integration of ethnomedicinal knowledge with modern scientific research holds the potential to revolutionize snakebite management, especially in regions with limited access to conventional antivenom. By combining the wisdom of traditional healers with the rigor of scientific inquiry, researchers can develop novel and effective treatments for this neglected tropical disease.

11.2. Comparative analysis of ethnomedicinal plant-based antivenom therapies

The global burden of snakebite envenomation underscores the urgent need for effective and accessible countermeasures. Traditional knowledge has long recognized the potential of medicinal plants to counteract snake venom, and recent research has begun to validate these claims. A comparative analysis of ethnomedicinal practices across different regions reveals a rich tapestry of plant-based therapies.

Africa, India, and Central America have been particularly prolific in documenting the use of medicinal plants for snakebite treatment. In Kenya, species such as *Conyza bonariensis, Commiphora africana*, and *Vernonia glabra* have demonstrated potent antivenom properties, particularly in inhibiting phospholipase A2 (PLA2), a key venom component [99]. Similarly, *Vitex negundo* from India has garnered significant attention for its ability to neutralize the lethal effects of *V. russelli* and *Naja naja* venoms [51]. Nigeria and Central America also offer promising examples of plant-based therapies, with species such as *Anogeisus leiocapus*, *Euphobia hirta*, *Ageratum conyzoide,* and *Brownea rosa*, -de-monte exhibiting antivenom activities [64,98].

These studies collectively highlight the diverse array of plant species employed for snakebite treatment across different geographical regions. The underlying principle often involves the utilization of secondary metabolites, such as flavonoids, alkaloids, and tannins, which possess potent antivenom properties. These compounds can inhibit key venom enzymes, reduce inflammation, and mitigate other systemic effects of envenomation.

While the evidence for the efficacy of these plant-based therapies is growing, further research is imperative to fully understand their mechanisms of action and to develop standardized formulations.

Comparative studies between different plant species and venom types can provide valuable insights into the potential of phytocompounds as broad-spectrum antivenom agents. Additionally, the isolation and characterization of the active compounds responsible for antivenom activity will facilitate the development of synthetic analogs and drug delivery systems.

In conclusion, the exploration of ethnomedicinal plants offers a promising avenue for the development of novel antivenom therapies. By combining traditional knowledge with modern scientific techniques, researchers can unlock the therapeutic potential of these natural resources and contribute to the global effort to combat snakebite envenomation.

11.3. From bench to bedside: clinical translation of phytotherapeutic antivenoms

While preclinical studies have provided compelling evidence for the efficacy of phytocompounds in neutralizing snake venom components, the ultimate goal is to translate these findings into safe and effective human therapies. The transition from bench to bedside necessitates rigorous clinical trials to evaluate the therapeutic potential and safety of plant-based antivenoms.

Numerous studies have demonstrated the efficacy of plant extracts in counteracting the lethal and pathological effects of snake venom in animal models. For instance, *Vitex negundo* has shown promise in neutralizing the venom of *V. russelli* and *Naja naja* [51], while African and American plant species have exhibited antivenom properties against various snake genera ([64,98]; Antonio *et al.,* 2022). These preclinical successes underscore the potential of phytocompounds as a valuable therapeutic resource.

However, the complex pathophysiology of snakebite envenomation and the potential for adverse effects necessitate careful evaluation in human subjects. Clinical trials are essential to establish the safety, efficacy, and optimal dosing regimens for plant-based antivenoms. Furthermore, head-to-head comparisons with conventional antivenoms can provide valuable insights into the relative benefits and limitations of each approach.

Several challenges hinder the advancement of phytotherapeutic antivenoms in clinical trials. These include the need for standardized plant materials, rigorous quality control, and the development of appropriate formulations. Additionally, the complex regulatory landscape for herbal medicines can pose significant hurdles. Nevertheless, the potential benefits of plant-based antivenoms, particularly in resource-limited settings, warrant concerted efforts to overcome these challenges.

By investing in clinical research and development, we can harness the power of ethnomedicinal knowledge to create effective and accessible treatments for snakebite envenomation. This requires collaboration between traditional healers, scientists, clinicians, and policymakers to bridge the gap between traditional practices and modern medicine. Ultimately, the successful translation of phytocompounds into clinical practice will have a profound impact on the lives of millions of people affected by snakebite.

12. Discussion

Snakebite envenomation continues to be a significant global health concern, particularly in tropical and rural regions where access to conventional antivenom treatments is often limited. This review provides an in-depth analysis of ethnomedicinal plants as potential adjunct therapies for snakebite treatment, focusing on their pharmacological properties, mechanisms of action, and how they complement conventional antivenoms. The findings underscore the necessity for integrating traditional remedies with modern biomedical approaches to overcome the limitations associated with current antivenoms.

A thorough examination of the existing literature reveals that a wide variety of plant species have been used in traditional medicine across different regions for snakebite treatment. These plants are rich in secondary metabolites such as flavonoids, alkaloids, tannins, and polyphenols, which are known for their antivenom properties. For instance, plant species like *Vitex negundo* and *Terminalia chebula* have been studied for their ability to neutralize venom toxins. The bioactive compounds found in these plants show great promise in counteracting the toxic effects of snake venom through several key mechanisms [51].

The therapeutic efficacy of ethnomedicinal plants in neutralizing snake venom stems from several biochemical mechanisms. A key mechanism is the inhibition of phospholipase A2 (PLA2), an enzyme responsible for the disruption of cellular membranes and the induction of necrosis and inflammation. Flavonoids and polyphenols found in plants such as *Vitex negundo* and *Indigofera pulchra* have been shown to chelate calcium ions that are necessary for PLA2 activation, thereby reducing venom-induced tissue damage [37].

Another significant mechanism is the antioxidant activity exhibited by many ethnomedicinal plants. Snake venoms, particularly those from viper species, induce oxidative stress through the generation of reactive oxygen species (ROS). Compounds in plants like *Vitex negundo* possess potent antioxidant properties that neutralize these free radicals, thereby minimizing oxidative tissue damage. This mechanism is critical in mitigating the progression of venom-induced pathologies such as necrosis, edema, and systemic organ failure [52].

Additionally, ethnomedicinal plants exert anti-inflammatory effects by modulating the body's immune response. Alkaloids and tannins found in plants such as *Andrographis paniculata* have been shown to reduce the secretion of pro-inflammatory cytokines. This helps to control excessive inflammation, one of the major causes of venom-induced morbidity, and alleviates symptoms such as swelling, pain, and tissue necrosis [50]. These anti-inflammatory effects are particularly important in regions where snakebite victims do not have immediate access to antivenom, as the phytocompounds can help mitigate the inflammatory response until proper treatment is administered.

In addition to inhibiting enzymes and reducing oxidative stress, some phytochemicals directly bind to venom toxins, neutralizing their harmful effects. Tannins from plants such as *Terminalia chebula* exhibit a strong affinity for venom proteins, preventing them from interacting with cellular targets. This direct binding blocks the venom from causing damage, similar to the mechanism of conventional antivenoms that target specific venom components [100]. The broad-spectrum binding ability of these phytochemicals also means that they may be effective against a wider array of venom types, including venoms from different species or those with variable compositions.

Ethnomedicinal plants also demonstrate the ability to modulate blood coagulation, which is often disrupted by snake venom, particularly from hemotoxic species like *Bothrops* and *Daboia*. Venoms from these snakes induce coagulopathies, leading to either excessive bleeding or blood clotting. Certain plants have shown the ability to stabilize platelet function and promote normal clotting pathways. For example, extracts from *Erythroxylum* species have demonstrated efficacy in reducing venom-induced hemorrhage by modulating coagulation factors [60]. This activity is particularly relevant for venoms that cause systemic bleeding or disrupt the clotting process.

Recent advancements in bioinformatics and nanotechnology have further propelled the development of plant-based therapies. Bioinformatics tools, such as molecular docking and simulation studies, have allowed researchers to explore the molecular interactions between phytocompounds and venom proteins. These computational methods have been instrumental in identifying lead compounds that can effectively inhibit venom toxins, thereby optimizing the drug discovery process [81]. Nanotechnology-based delivery systems, including nanoparticles and liposomal formulations, have also shown promise in enhancing the bioavailability and efficacy of phytocompounds. These systems protect the active compounds from degradation, ensuring that they reach their intended targets in the body with higher precision [84].

While the potential of ethnomedicinal plants as complementary therapies is clear, several challenges must be addressed before these therapies can be fully integrated into clinical practice. One major challenge is the standardization of plant extracts. The efficacy of phytocompounds can vary greatly depending on factors such as plant species, geographic origin, and the method of extraction. Comprehensive toxicity testing is also essential to ensure that these plant-based treatments are safe for human use. Furthermore, clinical protocols need to be developed to guide the use of these therapies alongside conventional antivenoms, particularly in terms of dosage, timing, and combination with other treatments.

Additionally, the complexity of snake venom itself poses a challenge to the use of plant-based therapies. Venom composition can vary not only between species but also within individuals of the same species, depending on factors such as age, diet, and geographic location [25]. Therefore, any plant-based therapy must be evaluated for its efficacy across a range of venom types to ensure its broad applicability.

13. Conclusion

This review highlights the potential of ethnomedicinal plants in antivenom development, advocating for the integration of traditional knowledge with modern science and addressing the urgent need for effective and accessible treatments for snakebite envenomation.

The integration of bioinformatics, nanotechnology, and clinical research is essential for translating the promise of phytocompounds into tangible clinical benefits. Future research should focus on identifying the bioactive compounds responsible for antivenom activity, optimizing drug delivery systems, and conducting well-designed clinical trials to evaluate the safety and efficacy of these therapies.

Moreover, there is a need for collaborative efforts between scientists, traditional healers, and policymakers to bridge the gap between traditional knowledge and modern medicine. By investing in research and development, we can harness the power of nature to combat the devastating effects of snakebite envenomation.

14. Potential impact

The findings of this review can inform the development of novel antivenom therapies, particularly in regions with limited access to conventional treatments. By highlighting the potential of phytocompounds as a valuable resource, this study encourages further research and investment in this area. Additionally, the integration of bioinformatics and nanotechnology offers promising avenues for improving the efficacy and safety of phytotherapeutic interventions. Ultimately, this research contributes to the global effort to reduce the burden of snakebite envenomation and improve the health and well-being of affected populations.

Future perspectives

Interdisciplinary Research: Bridging traditional ethnomedicinal knowledge with modern pharmacological and toxicological research is essential for the comprehensive understanding and validation of plant-based therapies against snake venom.

Standardization and Clinical Trials: There is a need for the standardization of plant extracts and formulations, followed by rigorous clinical trials to establish their safety, efficacy, and optimal dosages for snakebite treatment.

Conservation and Sustainable Use: With the increasing interest in ethnomedicinal plants, sustainable harvesting practices and conservation of biodiversity are paramount to ensure the availability of these valuable resources for future generations.

Global Collaboration: International collaboration among researchers, clinicians, and traditional healers can facilitate the sharing of knowledge, resources, and best practices in the treatment of snakebites.

Public Health Initiatives: Integrating the use of ethnomedicinal plants into public health strategies, especially in snakebite-prone regions, could enhance community resilience and preparedness against snakebite envenomation.

By addressing these future perspectives, we can harness the full potential of ethnomedicinal plants in complementing existing snakebite treatments, ultimately reducing the global burden of snakebite envenomation, and paving the way for more inclusive and accessible healthcare solutions.

CRediT authorship contribution statement

Sana Hussain: Writing – review & editing, Writing – original draft. **Danie Kingsley:** Writing – review & editing, Supervision.

Declaration of Competing Interest

None.

Data Availability

No data was used for the research described in the article.

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