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Medicinal plants for the treatment of snakebite envenoming: A Review

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Abstract
In Nigeria, particularly within the Savannah region, venomous snakebites are a major public health concern, often leading to high mortality rates and permanent disabilities. Snake venom is highly toxic and requires the immediate administration of antivenom, which remains the most effective and widely accepted therapy. However, the limitations of conventional antivenoms including high cost, restricted availability and poor accessibility have spurred growing interest in traditional medicine. In this context, small-molecule inhibitors derived from medicinal plants, historically used by traditional healers to counteract snake venom, are gaining renewed attention. Ethnobotanical surveys have revealed the use of numerous plants in snakebite treatment, reflecting their cultural and therapeutic significance. To identify these plants, highlight scientific advances, and uncover gaps in their application for antivenom development, a narrative review was conducted. Relevant publications on medicinal plants used in snakebite management were retrieved from various scientific databases and systematically reviewed. This review considers the ethnobotanical uses of medicinal plants in snakebite treatment, their botanical descriptions and phytochemistry, as well as empirical reports on documented species used against snake envenomation. Furthermore, it underscores the critical need for well-designed clinical trials to provide scientific validation and support the integration of these medicinal plants into modern therapeutic strategies.

Keywords: Envenomation, snakebites, antivenom, neutralize, therapy, ethnobotanical

Introduction
In tropical and subtropical countries, snakebite constitutes a neglected medical emergency usually resulting in an annual snakebite of about 5.4 million globally. According to the World Health Organization (WHO) (2023), snakebites affect millions of people worldwide each year, resulting in thousands of deaths and many more cases of long-term disability. The global burden of snakebites is estimated to be around 1.8 to 2.7 million envenoming cases annually, with approximately 81,000 to 138,000 deaths (Kasturiratne *et al.*, 2008, WHO, 2023) [34]. There is a wide disparity in the global distribution of snakebites, with Asia having the majority of cases followed by Africa and Latin America. In Asia, high numbers of snakebite cases are reported in India, Pakistan, and Sri Lanka, with mortality rates ranging from 2.4 to 20.4 per 100,000 population annually (Mohapatra *et al.*, 2011) [37]. In African countries such as Nigeria, South Africa, and Kenya, snakebites are a significant problem. In Nigeria, for instance, snakebites are a major public health issue, particularly in the rural areas, where there are activities that contribute largely to increased human snake interactions, such as farming and other rural practices (Abduljalil *et al.*, 2022) [1], with limited access to healthcare. A study (Habib *et al.*, 2015) [24] reported an incidence of 48.5 snakebites per 100,000 population per year, with a 10.3% mortality rate in Nigeria. In the Savannah area of Nigeria, there is a prevalent incident of snakebites with an average cases of 20,000 snakebites in the year 2020 alone, with mortality of about 2,000, and also 1,700 to 2,000 cases of arm and leg amputations (Abduljalil *et al.*, 2022) [1]. In Nigeria, there is a gross underestimation of the actual figures of snakebite incidence due to the fact that most of the intervention and treatment gotten from the traditional medicine practitioners are not documented, however, a single hospital reported within three years, snakebite-related cases of 6,687(Abduljalil *et al.*, 2022) [1].
There are over 600 species of venomous snakes, but few species of the several venomous snake species found worldwide are said to be medically important, because they call for immediate medical intervention, to save the life of the victims bitten by such species.

These "medically important" snakes are those with venom that can cause significant health effects, such as neurotoxicity, hemotoxicity, or tissue damage, and require specific treatment like antivenom. Examples of such medically important snakes include those belonging to the families of Elapidae (cobras, kraits, mambas, and coral snakes) whose venom is often neurotoxic, affecting the central nervous system and potentially leading to paralysis of the respiratory muscles, Viperidae (vipers, rattlesnakes, copperheads, cottonmouths**,** and pit vipers)**.** Their venom can cause a variety of effects, including tissue damage, blood clotting problems, and systemic effects like internal bleeding (Tednes and Slesinger, 2024) [57].

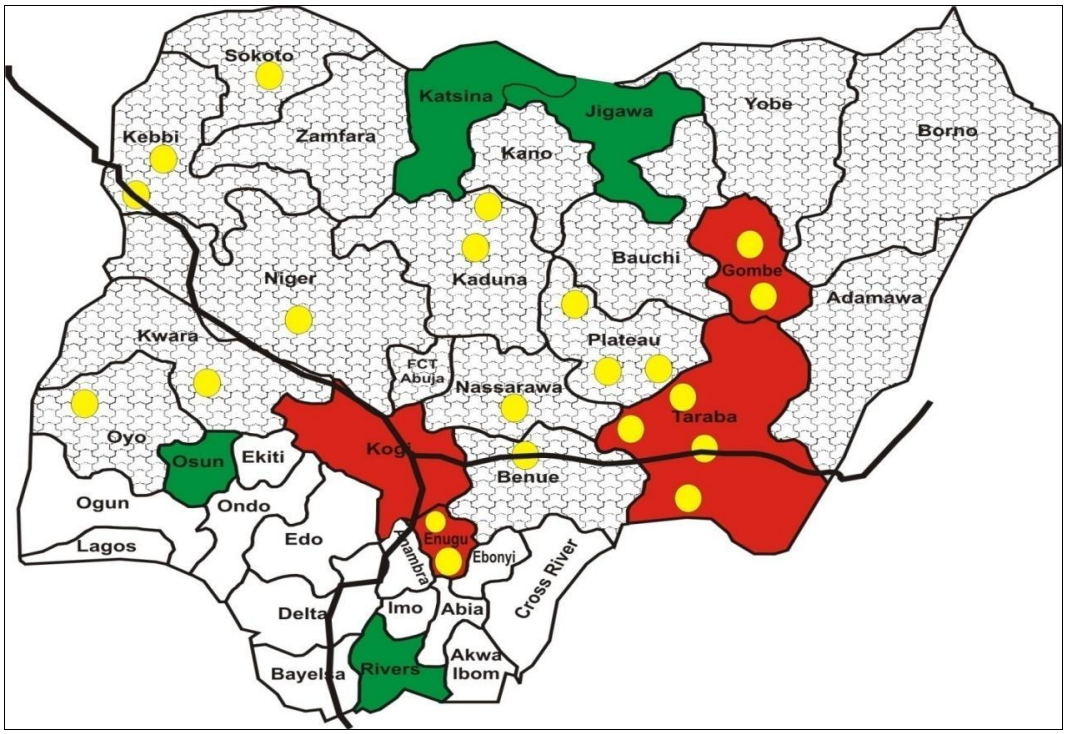

Fig 1: Map of Nigeria showing distribution of Snakes of Medico-Economic Importance

Key

- Yellow spots have published reports of *E. ocellatus*
- The shaded areas gives *E. ocellatus* habitat
- High prevalence states
- Low prevalence states

The venom from snakebites consists of different proportions of a mixture of enzymatic and non-enzymatic toxins. Due to certain factors such as species, age, sex, geographic location, the relative proportions of toxins differ (Tasoulis *et al.*, 2022, Casewell *et al.*, 2014) [15, 56]. Phospholipase A_2S (PLA_2S), metalloproteases (SVMP), serine proteases (SVSP), acetylcholinesterases (AChE), nucleotidases (5′-nucleotidases, phosphodiesterases, PDE; NT ATPases; and DNases), hyaluronidase (Hya), and L-amino acid oxidase (LAAO) are the most common snake venom from the proteomic studies, while the three-finger toxins (3FTx), Kunitz-type serine proteinase inhibitor (KSPI), cysteine-rich secretory proteins (CRISPs), snake C-type lectin-like proteins (snaclecs), and disintegrins constitute mainly the non-enzymatic venom toxins (Upasana et al, 2022 [60], Sanhajariya *et al.*, 2018) [50]. Furthermore, Doley & Kini (2009) [19] noted that more potent pharmacological activities are exhibited when non toxic proteins component of the venom form covalent/non-covalent complexes with other proteins. The lethal potency of the snake venom is thus enhanced by the synergistic interactions between the venom proteins.

Mukherjee and Mackessy (2021) [38] noted that immediate administration of bivalent or polyvalent antivenom is the most effective and accepted therapy against a venomous snakebite. Upasana et al (2022) [60], however, reported serum sickness, anaphylaxis and pyrogenic reactions in the treated patient as several adverse effects from the antivenom therapy. In addition to the several side effects, commercial antivenoms are not effective against all venomous snakes **(**often focused on neutralizing the "Big Four" venomous snakes (Russell's viper, Indian cobra, krait, and saw-scaled viper), leaving other species under-treated), limited effectiveness against local effects (antivenom may not effectively neutralize all venom components, especially those with lower molecular mass, which can be responsible for localized tissue damage), poor immunorecognition (some toxins in snake venom, particularly those with lower molecular mass, may be poorly recognized and neutralized by the antibodies in antivenoms), high cost making it non-accessible to the impoverished section of the society living in remotes areas, lack of basic cold storage facilities as well as lack of awareness thus making this therapy a serious concern (Patra *et al.*, 2021) [43]. Unfortunately, it is difficult to produce antivenom against all of a country's venomous snake species (Senji Laxme *et al.*, 2019) [52]. Based on the prior experiences and observations of the communities, many people depend primarily on herbal medicine and traditional healing practices for the treatment of envenomation. Procedures such as chewing leaves and bark, drinking plant extracts or any decoctions prepared from the extracts, and applying the plant or sap to the bite area are used to counteract snake envenomation (Upasana *et al.*, 2022). Generally, people treat snake envenomation using a single plant's parts or a combination of more than one plant's parts as antidotes. However, the scientific study of the efficacy of traditional snakebite therapy has not been carried out.

The limitation of conventional antivenoms has spurred interest in traditional medicine, where small-molecule inhibitors obtained from local medicinal plants or parts of the

plant have been historically used to counteract snake venom. These small molecule inhibitors can be stored conveniently without refrigeration in the rural health centers. Most importantly, the small molecule inhibitors have a broad neutralizing potential against major venom toxins across snake species, it is safe, affordable, easy to administer, without storage logistic problems, and have a promising potential for consideration as therapy for snakebite. Several plants are traditionally used in Nigeria and globally for the treatment of snake envenomation, with *Mucuna pruriens* (velvet bean) and *Allium sativum* (garlic) being among the most studied. Other notable plants include *Annona senegalensis*, *Nigella sativa*, and *Citrullus colocynthis*. This review therefore seek to identify medicinal plants used for the traetment of snake envenomin among the various people of Nigeria as well as the scientific progress made in developing envenomation from the medicinal plants through emperical review.

Methodology

The present review adopted a narrative review methodology. A review that attempt to summarize or synthesize existing literature on medicinal plants for snake envenomation without making generalization or cumulative knowledge from what is review. Rather, it aimed at providing the reader with comprehensive background for understating current knowledge and highlighting the significance of new research thus inspires research ideas by identifying inconsistencies or gap in medicinal plants research for snake envenomation (Pare and Kitsiou, 2016) [42]. Thus, to achieve this, published literature on medicinal plants for the treatment of snakebites from 2008 to 2025 was gathered from major scientific databases such as PubMed, ScienceDirect, Scopus, and Google Scholar. Keywords including *"snakebite envenomation," "medicinal plants," "antivenom activity," "traditional medicine,"* and *"phytochemicals"* were used in different combinations. Only peer-reviewed articles, ethnobotanical surveys, and experimental studies that provided information on the antivenom potential of medicinal plants were reviewed under various sections.

Ethnobotanical uses of medicinal plants in snakebite treatment: Traditional knowledge and cultural practices have long played a pivotal role in the treatment of snakebites, especially in regions where access to conventional medical care is limited. Across Africa, Asia, and Latin America, indigenous communities have developed extensive ethnobotanical knowledge, utilizing local flora to manage and treat snakebite incidents.

In Africa, numerous plant species are employed in traditional snakebite treatments. For instance, in Uganda, a study documented 60 plant species from 28 families used by traditional medicine practitioners (TMPs) for snakebite management. The most used plant parts were roots (42.6%) and leaves (25.0%), with preparations administered orally (61.2%) and topically (37.6%). Common preparation methods included cold water infusions (32.5%) and decoctions (21.7%) (Omara *et al.*, 2020) [41]. Similarly, in Tanzania, a systematic review highlighted that roots (54%) and leaves (26%) are the most frequently used plant parts in snakebite treatments. Decoction (23%) and crushing (22%) were common preparation techniques, with remedies administered topically (57%) and orally (43%) (Kacholi and Amir, 2022) [32].

In Asia, particularly in India, traditional medicine has incorporated plants like *Rauvolfia serpentina*, known for its use in treating snakebites, among other ailments (Dey and De, 2011) [17]. In Bangladesh, ethnomedicinal surveys have documented the use of 38 plant species by traditional healers, with *Aegle marmelos*, *Aristolochia indica*, and *Anisomeles malabarica* being among the most frequently cited other plants which was generally accepted among the users for its protective activity when administered for snakebite include *Rauwolfia serpentina L, Emblica officinalis Linn, Aristolochia indica L* and *Morinda citrifolia L* (Hasan *et al.*, 2016) [25].

In Latin America, traditional healers in Colombia utilize 71 plant species for snakebite treatment, with leaves (24.82%), stems (11.68%), and flowers (10.95%) being the most frequently employed structures in the preparation of extracts. These are usually prepared by decoction (83.94%) and maceration (6.57%) (Vásquez-Escobar *et al.*, 2015) [61]. In the Peruvian Amazon, the Cashinahua (Huni Kuin) people employ a comprehensive three-stage treatment for snakebites, involving external application of plant juices, bathing the affected part in herbal decoctions, and ingestion of small doses of the same remedy (Horackova *et al.*, 2023) [27].

In Nigeria, traditional knowledge of medicinal plants for snakebite treatment is deeply rooted in the cultural practices of various communities. Ethnobotanical surveys have documented the use of numerous plant species by different ethnic groups for managing snakebite envenomation. In the northwestern states of Sokoto, Kebbi, and Zamfara, a study identified 25 medicinal plant species employed by traditional healers to treat snakebites. Commonly used plant parts include roots and leaves, prepared through methods such as decoction and pounding, and administered orally or applied topically. Notable species include *Securidaca longepedunculata*, *Piliostigma thonningii*, and *Annona senegalensis* (Ibrahim-Maigandi *et al.*, 2020) [29].

Among the Fulani herdsmen in Taraba State, 19 plant species from 15 families have been reported for snakebite treatment, with *Annona senegalensis* being the most frequently used. The remedies are typically prepared by crushing or pounding plant parts and administered orally or applied to the bite site (Ameen *et al.*, 2015) [8].

In Benue State, the Idoma people utilize various plants for snakebite management. A survey recorded 18 plant species from 11 families, with the Fabaceae family being the most represented. Commonly used plants include *Schumanniophyton magnificum*, *Vitellaria paradoxa*, and *Ficus exasperata*. Preparation methods involve crushing or decocting plant parts, with administration routes being topical or oral (Nodza *et al.*, 2020) [39].

In southwestern Nigeria, particularly in the Saki and Ogbomoso agricultural zones, Fulani herdsmen have been documented using plants like *Securidaca longepedunculata* and *Piliostigma thonningii* for treating snakebite symptoms. The remedies are prepared by crushing or pounding plant parts and administered orally or applied topically (Akinmoladun *et al.*, 2022) [4]. These ethnobotanical practices underscore the significance of traditional knowledge in snakebite management, emphasizing the need for further research to validate the efficacy and safety of these medicinal plants.

Botanical description and phytochemistry of medicinal plants for snake envenomation: Medicinal plants have long been utilized in the treatment of snakebites, particularly in regions where snakebites are a significant public health concern. Numerous plant species have been documented for

their ability to neutralize venom toxins, providing a basis for traditional and complementary therapies. In global and local contexts, several plants stand out for their frequent citation in ethnobotanical and pharmacological studies due to their efficacy in managing envenomation.

The genus *Moringa*, particularly *Moringa oleifera* Lam. (family Moringaceae), is extensively distributed across tropical and subtropical regions. Its leaves and seeds have been reported to contain flavonoids, alkaloids, and tannins, which exhibit anti-inflammatory and antioxidant properties. These phytochemicals are thought to mitigate venom-induced oxidative stress and tissue damage. In Nigeria, *Moringa oleifera* is widely cultivated and has been traditionally used as an adjunct treatment for snakebites (Adeyi *et al.*, 2021) [2].

Andrographis paniculata (Burm. f.) Nees (family Acanthaceae) is another globally recognized species. Native to South and Southeast Asia, this plant's phytochemical profile includes diterpenoids, flavonoids, and polyphenols. Studies have shown that its diterpenoid compound, andrographolide, inhibits enzymatic components of snake venom such as phospholipase A2, reducing systemic toxicity (Shivashankar *et al.*, 2019) [54].

The *Curcuma* genus, particularly *Curcuma longa* L. (family Zingiberaceae), is a widely studied plant with global distribution in tropical regions. Its rhizome contains curcuminoids, including curcumin, which have demonstrated venom-neutralizing properties by inhibiting oxidative damage and inflammation (Ghosh and Gomes 2016; Ramadas *et al.*, 2024) [23, 46]. In Nigeria, turmeric is gaining recognition in traditional medicine for similar applications.

Garcinia kola Heckel (family Clusiaceae), commonly known as bitter kola, is indigenous to West Africa and highly valued in Nigerian ethnomedicine. Its seeds are rich in biflavonoids, xanthones, and phenolic compounds, which are believed to stabilize cell membranes and counteract venom-induced hemotoxic effects (Fidele *et al.*, 2022) [21].

Azadirachta indica A. Juss. (family Meliaceae), or neem, is a plant with pan-tropical distribution, including Nigeria. Extracts from its leaves and bark contain limonoids and quercetin derivatives. These compounds exhibit anti-inflammatory and cytoprotective activities, making them relevant in neutralizing cytotoxins in snake venom (Sani *et al.*, 2020) [48].

Acacia nilotica (L.) Willd. ex Delile (family Fabaceae) is another species cited for its medicinal use in snakebite treatment. Distributed widely in Africa and parts of Asia, its bark and gum contain tannins and proanthocyanidins. These compounds have been shown to inhibit venom-induced coagulopathies (Sarje *et al.*, 2020) [5].

Carica papaya L. (family Caricaceae) is a fruit-bearing plant native to the tropics and widely cultivated in Nigeria. Its latex and seeds are rich in proteolytic enzymes such as papain, which decompose venom proteins, reducing their toxic effects (Balaramnavar, 2020) [11].

Euphorbia hirta L. (family Euphorbiaceae) is commonly found in tropical and subtropical regions, including Nigeria. Its bioactive compounds, including terpenoids and alkaloids, have demonstrated efficacy in neutralizing neurotoxins in venom (Meda *et al.*, 2023) [36].

The genus *Pluchea*, specifically *Pluchea indica* (L.) Less. (family Asteraceae), is a traditional antidote for envenomation in Asia. Its leaves contain sesquiterpenes and polyphenols that counteract inflammatory responses induced by venom (Ahemd & Kamel, 2013; Ibrahim *et al.*, 2022) [30].

Aristolochia species, including *Aristolochia indica* L. (family Aristolochiaceae), are notable for their ethnopharmacological relevance. Distributed in South Asia and Africa, these plants' roots are rich in aristolochic acids, which show inhibitory activity against metalloproteases in venom (Borah *et al.*, 2021; Samy *et al.*, 2008) [14, 47]. However, caution is necessary due to their nephrotoxic potential.

Vitex doniana Sweet (family Lamiaceae), native to Africa, is widely used in Nigerian traditional medicine. Its leaves and bark contain flavonoids and iridoids that stabilize cell membranes and counteract the myotoxic effects of venom (Irampagarikiye *et al.*, 2025) [31].

Ocimum gratissimum L. (family Lamiaceae), known as scent leaf in Nigeria, contains eugenol and other phenolic compounds in its leaves. These bioactives exhibit anti-inflammatory and enzyme-inhibitory properties relevant to venom neutralization (Bhavani *et al.*, 2019; Sandeep, 2017) [13, 49].

The cactus-like plant *Opuntia ficus-indica* (L.) Mill. (family Cactaceae) is a global species used in traditional medicine. Its cladodes and fruits are rich in betalains and flavonoids that mitigate venom-induced oxidative stress (El-Mostafa *et al.*, 2014; Raj *et al.*, 2023) [20, 45].

Acalypha indica L. (family Euphorbiaceae) is widely distributed in tropical Africa, including Nigeria. Its leaves contain bioactive compounds such as alkaloids and tannins, which demonstrate venom protein-inhibitory activity (Chekuri *et al.*, 2020) [16].

Annona senegalensis L. (family Annonaceae) also known as wild custard apple or wild soursop is native to the tropical Africa, including Nigeria. Its seeds and leaves are rich in acetogenins and alkaloids that counteract venom's cytotoxic effects (Akpan *et al.*, 2016; Hassan *et al.*, 2022; Babalola *et al.*, 2021) [5, 10, 26].

Zanthoxylum zanthoxyloides (Lam.) Zepern. & Timler (family Rutaceae), commonly known as chewing stick, is native to West Africa. Its root bark contains alkaloids, coumarins, and essential oils, which are effective in mitigating venom-induced neurotoxic effects (Bandé *et al.*, 2025; Olushola-Siedoks *et al.*, 2020) [12, 40].

Calotropis procera (Aiton) Dryand. (family Apocynaceae) is a widely distributed plant in Africa and Asia. Its latex contains proteolytic enzymes that degrade venom proteins, reducing their toxic effects (Tiwari & Singh, 2025) [59].

Hibiscus sabdariffa L. (family Malvaceae) is cultivated globally and in Nigeria for its medicinal and nutritional value. Its calyces contain anthocyanins and flavonoids that scavenge free radicals induced by venom toxins (Abduljalil *et al.*, 2022; Deshpande *et al.*, 2022; Marina, 2024) [1, 18, 35].

In summary, these medicinal plants' rich phytochemical diversity provides a basis for their therapeutic efficacy against snakebites. Their global and local distribution highlights their accessibility and relevance in traditional medicine systems. Continued research into these plants' bioactive compounds is essential for developing novel antivenom therapies.

Over recent decades, researchers from Africa, Asia, Latin America, and beyond have undertaken empirical investigations ranging from ethnobotanical surveys to *in vitro* and *in vivo* studies to validate the potential of these plants as potential antivenom agents. This review synthesizes key findings from empirical studies, highlighting the geographical context, background, methodologies, and outcomes, as well as the challenges that remain.

Table 1: Summary of Botanical Description and Phytochemistry of Medicinal Plants for Snake Envenomation

Species	Family	Part used	Key phytochemicals	Antivenom-relevant activities	Representative references
Moringa oleifera	Moringaceae	Leaves, seeds	Flavonoids, phenolic acids, isothiocyanates	Antioxidant, anti-inflammatory, membrane-stabilizing	Adeyi *et al.*, 2021[2]
Andrographis paniculata	Acanthaceae	Aerial parts	Andrographolide, neoandrographolide	Anti-inflammatory, PLA2/COX inhibition	Shivashankar *et al.*, 2019 [54]
Curcuma longa	Zingiberaceae	Rhizome	Curcumin, demethoxycurcumin	Antioxidant, venom enzyme inhibition *in vitro*	Ghosh and Gomes 2016; Ramadas *et al.*, 2024[23]
Garcinia kola	Clusiaceae	Seeds	Biflavonoids (kolaviron), garcinol	Antioxidant, anti-inflammatory, enzyme inhibition	Fidele *et al.*, 2022[21]
Azadirachta indica	Meliaceae	Leaves, seeds, bark	Limonoids, quercetin	Antioxidant, anti-inflammatory, wound-healing	Sani *et al.*, 2020 [48]
Acacia nilotica	Fabaceae	Bark, gum	Tannins, proanthocyanidins	Astringent, antioxidant, coagulopathy modulation	Sarje *et al.*, 2020[51]
Carica papaya	Caricaceae	Latex, seeds	Cysteine proteases, phenolics	Proteolysis of venom proteins, anti-inflammatory	Balaramnavar, 2020 [11]
Euphorbia hirta	Euphorbiaceae	Whole plant, leaves	Flavonoids, tannins, triterpenes	Antioxidant, anti-inflammatory, edema reduction	Meda *et al.*, 2023[36]
Pluchea indica	Asteraceae	Roots, leaves	Sterols, flavonoids	Neutralizes lethality, hemorrhage, edema (direct evidence)	Ahemd & Kamel, 2013; Ibrahim *et al.*, 2022 [30]
Aristolochia indica	Aristolochiaceae	Root	Aristolochic acids, lignans	Ethnomedicinal antivenom use; nephrotoxic risk	Borah *et al.*, 2021; Samy *et al.*, 2008 [14, 47]
Vitex doniana	Lamiaceae	Leaves, bark	Flavonoids, phenolics, iridoids	Antioxidant, membrane-stabilizing, anti-inflammatory	Irampagarikiye *et al.*, 2025 [31]
Ocimum gratissimum	Lamiaceae	Leaves	Eugenol, rosmarinic acid, thymol	Antioxidant, PLA2/COX inhibition, tissue protection	Bhavani *et al.*, 2019; Sandeep, 2017 [13, 49]
Opuntia ficus-indica	Cactaceae	Cladodes, fruits	Betalains, flavonoids	Antioxidant, cytoprotective; no direct venom data	El-Mostafa *et al.*, 2014; Raj *et al.*, 2023 [20, 45]
Acalypha wilkesiana	Euphorbiaceae	Leaves	Flavonoids, tannins, triterpenes	Antioxidant, antimicrobial, anti-inflammatory	Chekuri *et al.*, 2020 [16]
Annona senegalensis	Annonaceae	Leaves, fruit	Phenolics, flavonoids, acetogenins	Antioxidant, anti-inflammatory, ROS protection	Akpan *et al.*, 2016; Hassan *et al.*, 2022; Babalola *et al.*, 2021[5, 10, 26]
Zanthoxylum zanthoxyloides	Rutaceae	Root bark	Alkaloids, coumarins, essential oils	Enzyme inhibition, membrane stabilization, ethnomedicinal	Bandé *et al.*, 2025; Olushola-Siedoks *et al.*, 2020[12, 40]
Calotropis procera	Apocynaceae	Latex, leaves	Proteases, cardiac glycosides, flavonoids	Proteolysis of venom proteins, anti-inflammatory (toxic latex)	Tiwari & Singh, 2025 [59]
Hibiscus sabdariffa	Malvaceae	Calyces	Anthocyanins, flavonoids	Strong antioxidant, oxidative stress mitigation	Abduljalil *et al.*, 2022; Deshpande *et al.*, 2022; Marina, 2024 [1, 18, 35]

Empirical review of some documented medicinal plants for the treatment of snake envenoming

Tijani *et al.* (2023) [58] conducted Kinetic Study of the Effect of Vernonia amygdalina Leaf Extract against *Echis ocellatus* Venom Hyaluronidase. The primary research was conducted at the Department of Biochemistry, University of Maiduguri, Maiduguri, Nigeria. Collaborative work also involved researchers from Usmanu Danfodiyo University, Sokoto, Nigeria and the Laboratory of Venoms and Toxins at the Pasteur Institute of Morocco. The study investigates the kinetic interaction between the methanol extract of *Vernonia amygdalina* leaves and hyaluronidase from *Echis ocellatus* venom. By exploring how the extract interferes with the enzymatic activity of hyaluronidase, the researchers aim to provide a mechanistic foundation for its traditional antivenom use. The study in its methodology employed a series of biochemical assays to elucidate the inhibitory effect of *Vernonia amygdalina* leaf extract on venom hyaluronidase. The leaves were processed using methanol extraction to isolate the active phytochemical constituents. The kinetic interaction was investigated using a modified Ellman colorimetric method, which is typically used to monitor enzyme activity by measuring changes in absorbance as the substrate is hydrolyzed. The effect of the extract on hyaluronidase activity was evaluated over a range of doses. A Dixon plot was then constructed to determine the inhibitory constant (Ki) and the nature of the inhibition. The study identified that the inhibition caused by *Vernonia amygdalina* was uncompetitive in nature-that is, the inhibitor binds only to the enzyme-substrate complex. A dose-dependent effect was observed, and the calculated IC_{50} (the concentration at which the enzyme activity is reduced by 50%) was determined to be 18.78 µM. The study found that, the methanol extract of *Vernonia amygdalina* leaves exhibits an uncompetitive inhibition of *Echis ocellatus* venom hyaluronidase. This indicates that the active compounds in the extract bind to the enzyme once the substrate has already been bound, reducing its catalytic activity. The inhibition is dose dependent, as demonstrated by a clear decrease in enzyme activity with increasing concentrations of the extract. The established IC_{50}

value of 18.78 µM reflects the extract's potency in neutralizing the enzyme's action. Since hyaluronidase facilitates the rapid spread of venom toxins, its inhibition could potentially slow venom dispersion and mitigate local tissue damage. These findings support the traditional use of *Vernonia amygdalina* as an antivenom agent and provide a biochemical basis for its therapeutic effects. This research not only validates ethnobotanical practices but also paves the way for further phytochemical characterization and potentially clinical trials aimed at standardizing and optimizing plant-based antivenom therapies.

In another study, inhibition of toxic effects of vipers and cobra venom by Indian medicinal plants by Alam (2014) [6]. The work was carried out under the auspices of the Department of Paramedical Sciences at Hamdard Institute of Medical Sciences & Research, Jamia Hamdard University in New Delhi, India. The study seeks to evaluate whether specific plant extracts could counteract the toxic effects elicited by venom from both vipers (such as *Daboia russelii* and *Echis carinatus*) and cobras (including *Ophiophagus hannah* and *Naja kaouthia*). The work builds on previous reports using methanolic extracts of plants like *Pluchea indica*, *Hemidesmus indicus*, *Vitex negundo*, and *Emblica officinalis* that showed promising antidote properties. The study undertook both *in vitro* and *in vivo* experiments to examine the antisnake venom efficacy of selected Indian medicinal plants. The investigation focused on four plant extracts derived from *Curcuma aromatica*, *Aristolochia indica*, *Andrographis paniculata*, and *Curcuma zeodaria*. These were chosen based on their traditional use and prior evidence of venom neutralizing activity. In the *In vitro* analysis, the extracts were first tested for their ability to neutralize key venom-induced enzymatic activities. The assays measured parameters such as phospholipase A_2 (PLA_2) activity, which is pivotal in venom-induced cytotoxicity, as well as other enzymatic activities (e.g., proteolytic and coagulant effects). Animal models were used to evaluate the protection conferred by the extracts against venom-induced lethality and pathophysiological changes. These tests included monitoring hemorrhagic activity, coagulant and defibrinogenating effects of *Daboia russelii* venom. An interesting facet of the work was the observation that, upon mixing venom with the plant extracts, no precipitating bands formed. This suggests that the active constituents are likely to neutralize toxins through selective binding or enzyme inhibition rather than through non-specific precipitation. The study found that the selected plant extracts have multiple venom neutralization effects, effective across venom types and mechanism of action considerations. The promising neutralization results provided by these extracts pave the way for deeper investigations, understanding their precise mechanisms of venom inhibition, and optimizing extract formulations for clinical use.

Shekins (2014) [53], in their study of anti-venom activity of *Mucuna pruriens* leaves extract against cobra snake (*Naja hannah*) venom seek to determine whether this extract can restore normal physiological biochemical parameters in envenomated animals and to compare its effects against the standard antivenin treatment. The study was designed as an *in vivo* investigation using mice as the experimental subjects. The mice were randomly divided into six groups (labeled A, B, C, D, E, and F), with each group consisting of five rats.

- **Group A:** Normal control (no venom induction; administered normal saline at 1 ml/kg body weight).
- **Group B:** Test control (envenomated with cobra snake venom but without treatment).
- **Group C:** Standard control (envenomated and treated with conventional antivenin).
- **Groups D, E, and F:** Envenomated groups treated with different doses of the ethanolic extract of *Mucuna pruriens* leaves (40 mg/kg, 60 mg/kg, and 80 mg/kg, respectively), administered intraperitoneally.

Cobra snake venom was administered at a dose of 0.075 mg/kg body weight to induce envenomation and Treatment with the plant extract was carried out daily over a period of 14 days. After the 14-day treatment, serum was collected from the animals to assay several biochemical parameters altered by venom toxicity, including: Total cholesterol, Bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Glutathione (GSH) and Catalase levels. The finding revealed that in the test control group (Group B), envenomation with cobra venom led to marked increases in cholesterol, AST, ALT, bilirubin, catalase, and glutathione levels (Shekins, 2014) [53]. These alterations indicate significant systemic toxicity and oxidative stress caused by the venom. Treatment with the ethanolic extract of *Mucuna pruriens* leaves (Groups D, E, and F) resulted in a significant reduction in the elevated biochemical markers compared to the test control group. The reduction was dose-dependent, with the highest efficacy observed at 80 mg/kg (Group F). Interestingly, the data suggests that the 80 mg/kg dose of *Mucuna pruriens* extract demonstrated a greater ability to restore key biochemical parameters to near-normal levels than the standard antivenin treatment (Group C). This indicates that the plant extract may possess potent anti-venom activity with an efficacy that could surpass the conventional antivenom in certain respects. These findings lay the groundwork for further studies focused on characterizing the bioactive compounds responsible for the observed antivenom activity, as well as advancing towards clinical trials to assess safety and efficacy in human subjects.

In a similar study Ameh et al, (2020) [7] conducted a study on the Detoxifying Action of Aqueous Extracts of *Mucuna pruriens* Seed and *Mimosa pudica* Root against Venoms of Naja nigricollis and Bitis arietans. The study was undertaken in Nigeria, with the primary affiliation being the Department of Veterinary Pharmacology and Toxicology at Ahmadu Bello University, Zaria, Nigeria. Additional collaborations include researchers from the Department of Pharmacology and Therapeutics at the same institution and the Queensland Brain Institute at The University of Queensland, Brisbane, Australia. The research aims to validate the traditional claims regarding these botanicals by evaluating their effects on key venom induced activities (i.e., fibrinolytic, haemolytic, and phospholipase A_2 activities) in an *in vitro* setting. Such work not only bridges ethnomedicinal practices with modern pharmacological research but also offers a promising basis for developing adjunct or alternative snakebite therapies. The study follows a systematic preclinical approach, incorporating several key experimental components:

Phytochemical Analysis and Preparation

a) **Extraction:** Aqueous extraction methods were used to prepare the plant extracts from *Mucuna pruriens* seed and *Mimosa pudica* root, ensuring that water-soluble bioactive compounds could be assessed.

b) **Phytochemical Screening:** Prior to biological testing, the extracts were qualitatively analyzed to determine their bioactive constituents. This step helps correlate their chemical profiles with predicted detoxifying activities.

Evaluation of Venom Toxicity Neutralization

a) **Fibrinolytic Activity Assay:** The extracts were tested for their ability to neutralize the fibrinolytic activity of the venoms. At a concentration of 50 mg/ml, both plant extracts were evaluated against the venom of *Naja nigricollis*, while for *Bitis arietans* venom, a significantly higher concentration (400 mg/ml) was required for similar neutralization.

b) **Haemolytic Activity Assay:** The researchers measured the capability of the extracts to suppress the haemolysis induced by venom. At 50 mg/ml, the *Mucuna pruriens* extract could inhibit haemolysis by approximately 70% for *Naja nigricollis* venom, whereas the *Mimosa pudica* extract achieved a reduction of around 49.4%.

c) **Phospholipase A_2 (PLA_2) Activity Assay**: The extracts' influence on venom PLA_2 activity was also examined. It was found that *Mucuna pruriens* extract, at 50 mg/ml, inhibited PLA_2 activity modestly by about 7.7%, while *Mimosa pudica* extract exhibited a somewhat better inhibitory effect recording approximately 23% inhibition at higher concentrations (e.g., around 200 mg/ml). Notably, further increases in the concentration of *Mucuna pruriens* extract (up to 400 mg/ml) did not produce additional inhibition for PLA_2 activity.

Overall *in vitro* Experimental Design

The study used these comparative assays to assess the direct detoxifying properties of the plant extracts on the enzymatic and cytotoxic activities induced by the two snake venoms. The results were analyzed to determine the effective concentrations and the relative potencies of the extracts against distinct venom activities. The study found that:

a) Both aqueous extracts demonstrated the capacity to neutralize the fibrinolytic effects of *Naja nigricollis* venom effectively at a low concentration (50 mg/ml). However, *Bitis arietans* venom required a much higher concentration (400 mg/ml) to achieve neutralization, suggesting differences in venom composition and the potency of the detoxifying agents against varying venom types

b) In haemolytic assays, the *Mucuna pruriens* seed extract was particularly effective reducing venom-induced haemolysis by 70% at 50 mg/ml while the *Mimosa pudica* root extract provided moderate protection by reducing haemolysis by 49.4% at the same concentration. This result highlights the potential of *M. pruriens* as a more robust inhibitor of haemolytic activity in the context of venom toxicity.

c) The extracts had only modest inhibitory effects on PLA_2 activity. *Mucuna pruriens* extract showed minimal inhibition (7.7% at 50 mg/ml) even when increased to higher concentrations, while *Mimosa pudica* extract afforded a better inhibition (23%), albeit at a higher effective concentration. This suggests that while both extracts possess detoxifying abilities, their influence on PLA_2 an important enzyme in venom cytotoxicity is less pronounced compared to their effects on fibrinolytic and haemolytic activities.

These findings not only validate centuries-old ethnomedicinal practices but also provide a promising platform for further research. Future studies should aim to optimize extraction techniques, and eventually progress to *in vivo* and clinical evaluations. Such advancements could ultimately lead to the development of standardized, effective, and affordable plant-based formulations for snakebite management.

Sani *et al.*, (2020) [48] also conducted a study on the Lethality of Naja nigricollis Reinhardt venom, and antivenom activity of Azadirachta indica A. Juss. leaf extracts on albino rats with the aim to determine the lethal doses (LD_{50} and LD_{100}) of *Naja nigricollis* (black-necked spitting cobra) venom and evaluate the *in vivo* efficacy of neem leaf extracts (both as a crude methanol extract and its solvent fractions) as potential antivenom agents in albino rats. The study employed several key experimental procedures:

Venom Lethality Determination

The researchers first established the venom's toxicity profile by determining its lethal doses in albino rats. They reported an LD_{50} of 0.389 mg/kg and an LD_{100} of 3.891 mg/kg body weight. Accurate quantification of these doses was critical for subsequent neutralization assays.

Preparation of Azadirachta indica Extracts

a) **Extraction:** Neem leaves were extracted using methanol, a solvent effective for recovering a wide range of bioactive compounds.

b) **Solvent Fractionation:** The crude methanol extract was further partitioned into hexane and ethyl acetate fractions, potentially enriching different classes of phytochemicals.

***In vivo* Antivenom Screening**

a) The antivenom activity of the crude extract and its fractions was assessed by pre-treating envenomated albino rats. After administering the lethal dose (LD_{100}) of the venom, treated groups received either the crude extract or one of its fractions.

b) **Outcome Measures:** The primary endpoint was the mean survival time of the treated animals. The crude methanol extract, the hexane fraction, and the ethyl acetate fraction all significantly increased survival time compared to venom-only (control) groups.

Data Analysis

Survival times were statistically compared among the treatment groups. For instance, the crude methanol extract produced a mean survival time of approximately 22.51 ± 2.38 hours, while the hexane and ethyl acetate fractions yielded mean survival times of around 23.68 ± 0.89 hours and 21.98 ± 1.36 hours, respectively. These values indicate that all extracts had a protective effect, with slight variations in efficacy across fractions.

The study effectively quantified the lethality of *Naja nigricollis* venom with an LD_{50} of 0.389 mg/kg and an LD_{100} of 3.891 mg/kg, validating the venom's potency. The crude methanol extract demonstrated notable antivenom activity by significantly extending the survival time of envenomated rats. Solvent fractions, both the hexane and ethyl acetate fractions exhibited robust protective effects. In particular, the hexane fraction showed a slightly longer mean survival time than the crude extract and the ethyl acetate fraction. Their work demonstrates that both crude methanol extracts and refined solvent fractions can prolong the survival of albino rats challenged with lethal doses of *Naja nigricollis* venom. This study not only validates traditional medicinal claims regarding neem's antidote potential but also underscores the importance of exploring plant-based therapies as safer, accessible, and cost-effective alternatives to conventional serum-based antivenoms. The study paves way for standardizing extract preparations and ultimately advancing to clinical trials to assess safety and efficacy in human subjects.

Challenges

Challenges associated with investigating plant-based antivenom therapies stem from the complexity of venom composition and the diverse mechanisms by which snake venom exerts its toxic effects. Snake venoms contain a wide range of enzymes and proteins, such as phospholipases, metalloproteases, and neurotoxins, each contributing to distinct pathological outcomes. Plant-derived bioactive compounds may interact selectively with certain venom components, leaving others un-neutralized (Silva *et al.*, 2023) [55]. Furthermore, the variability in venom composition between snake species and even within populations of the same species complicates the standardization of plant-based treatments. Another significant challenge is the lack of harmonized protocols for testing the efficacy and safety of plant-derived antivenom compounds, which limits the comparability of studies and hinders the development of universal therapeutic formulations (Anholeti *et al.*, 2021) [9].

Limitations

The limitations of current research also include the reliance on *in vitro* assays, which may not accurately replicate complex physiological responses to snake envenomation. *In vivo* studies, though more representative of real-world scenarios, are often constrained by ethical considerations and logistical challenges, such as the availability of suitable animal models. Additionally, plant bioactive compounds can exhibit poor bioavailability and stability in systemic circulation, limiting their therapeutic potential unless optimized through advanced drug delivery systems (Kaplan *et al.*, 2022) [33]. Traditional extraction methods, while simple and cost-effective, may not isolate the full spectrum of bioactive constituents, potentially reducing the efficacy of plant extracts compared to their whole plant counterparts (Pietroluongo *et al.*, 2023) [44].

Gaps and future directions

Research gaps include the limited understanding of synergistic interactions between plant-derived compounds and their molecular targets in venom components. While some plants have been extensively studied for their antivenom potential, others remain underexplored despite promising ethnobotanical evidence. Additionally, there is a scarcity of studies investigating the long-term safety and efficacy of plant-based antivenom treatments in human populations. Most research focuses on acute effects, with minimal attention to potential adverse effects or long-term outcomes (Hussain and Kingsley, 2024) [28]. Future studies should prioritize high-throughput screening of underexplored plant species, guided by ethnobotanical knowledge, to identify novel bioactive compounds. Furthermore, integrating omics technologies, such as proteomics and metabolomics, can enhance our understanding of the molecular mechanisms underpinning plant-venom interactions (Fuly *et al.*, 2025) [22].

To address these challenges, future research should also focus on optimizing plant extraction and purification techniques to enhance the yield and potency of bioactive compounds. Collaborative efforts involving multidisciplinary teams, including ethnobotanists, pharmacologists, and clinicians, are essential to bridge the gap between traditional knowledge and modern drug development. Expanding clinical trials to evaluate the safety and efficacy of promising plant-based therapies in diverse human populations will be crucial for translating laboratory findings into effective antivenom treatments. Moreover, exploring novel drug delivery systems, such as nanoparticle-based formulations, may overcome limitations related to bioavailability and stability, paving the way for more effective and accessible plant-based antivenoms (Hussain and Kingsley, 2024) [28].

Conclusion

The global burden of snakebite envenoming necessitates a multifaceted approach involving traditional knowledge and modern pharmacological research. Medicinal plants have emerged as promising candidates for the development of novel anti-snake venom agents due to their bioactive compounds with neutralizing effects on venom toxins. This review highlighted several plants that are frequently cited for their efficacy in managing envenomation, including *Moringa oleifera*, *Andrographis paniculata*, *Curcuma longa*, and *Garcinia kola*. These plants exhibit a range of phytochemicals such as flavonoids, alkaloids, tannins, and proteolytic enzymes, which demonstrate venom-neutralizing properties through mechanisms like antioxidant activity, enzymatic inhibition, and cytoprotection.

The importance of medicinal plants as potential sources of novel therapeutics cannot be overstated. Their accessibility, cultural relevance, and proven efficacy in traditional medicine systems provide a strong foundation for further investigation. By bridging ethnobotanical knowledge with advanced pharmacological studies, researchers can isolate and characterize bioactive compounds, paving the way for the development of cost-effective and sustainable antivenom therapies. The integration of these natural products into modern medical frameworks offers hope for addressing the significant morbidity and mortality associated with snakebite envenoming globally.

Conflict of interests

The authors have no conflict of interests to declare

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