frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 12 March 2025
DOI 10.3389/fphar.2025.1548929

OPEN ACCESS

EDITED BY
Da-Cheng Hao,
Dalian Jiaotong University, China

REVIEWED BY
Rehana Masood,
Shaheed Benazir Bhutto Women University, Pakistan
Vishal Patil,
R. C. Patel Institute of Pharmaceutical Education and Research, India

*CORRESPONDENCE
Ashish Kumar,
profbanjaraashish@gmail.com
Rameshwari A. Banjara,
rameshwaribanjara@gmail.com

RECEIVED 20 December 2024
ACCEPTED 12 February 2025
PUBLISHED 12 March 2025

CITATION
Kumar A, Banjara RA, Aneshwari RK, Khan J and Bernarde PS (2025) A comprehensive review on recent advances in the use of ethnomedicinal plants and their metabolites in snake bite treatment.
Front. Pharmacol. 16:1548929.
doi: 10.3389/fphar.2025.1548929

A comprehensive review on recent advances in the use of ethnomedicinal plants and their metabolites in snake bite treatment

Ashish Kumar[1]*, Rameshwari A. Banjara[2]*, Roman Kumar Aneshwari[3], Junaid Khan[4] and Paulo Sergio Bernarde[5]

[1]Department of Biotechnology, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India, [2]Department of Chemistry, Rajeev Gandhi Government Postgraduate College, Ambikapur, Chhattisgarh, India, [3]School of Pharmacy, MATS University, Raipur, Chhattisgarh, India, [4]Department of Pharmacy, Sant Gahira Guru Vishwavidyalaya, Sarguja Ambikapur, Chhattisgarh, India, [5]Laboratório de Herpetologia, Centro Multidisciplinar, Campus Floresta, Universidade Federal do Acre, Cruzeiro do Sul, Acre, Brazil

Snakebites are a severe medical and social issue, particularly in tropical and subtropical countries with minimal medical facilities, where the most dangerous snakes are found. Worldwide, most rural areas use medicinal plants alone or in combination as antidotes for snakebite treatment. Local knowledge of medicinal plants for snakebite treatment plays a more critical role in primary healthcare services in rural areas. As a result of this review, it is revealed that 39% of herbs, 38% of shrubs, 18% of trees, 2% of climbers, 2% of bulbs, and 1% of ferns have snake antivenom potential, which is indicative of the presence of numerous phytochemicals such as alkaloids, coumarins, curcuminoids, flavonoids, steroids, triterpenoids, and cinnamic acid in particular plants. According to the availability of information, the data focus on the plants, their families, and their parts from various literature sources. In the future, the valuable plants reported here and their phytoconstituents may be potential sources for developing effective natural drugs for snake bite treatments. Therefore, this review is a comprehensive study of the snake antivenom potential of various medicinal plants and their bioactive compounds.

KEYWORDS

snakebite, snake venom, ethnomedicine, medicinal plants, phytoconstituents

1 Introduction

Snake bites are a public health hazard; according to a World Health Organization (WHO) estimate (World Health Organization, 2021), up to 2.5 million instances of envenomation are caused yearly by snakebites. In many developing countries, snakebite is a severe issue, i.e., India is the country where the most number of snake bites occurs; the number of bites reaches about one million per year with about 600,000 envenomations and 58,000 deaths per year (Suraweera et al., 2020). The most commonly used therapeutic agent for snakebite treatment is the antiserum (antivenom), which is conventionally prepared by injecting a non-lethal quantity of snake venom into mammals such as rabbits and horses to

raise immunoglobins against snake venom, followed by separation of serum containing the immunoglobins from the mammal's blood (Makhija and Khamar, 2010) In addition to several studies, plant substances have been recognized as a good source of snake venom neutralization and claimed to be an antidote for snakebite treatment (Houghton and Skari, 1994; Abubakar et al., 2000). Numerous *in vitro* and *in vivo* studies reported in the literature that bioactive metabolites extracted and produced from medicinal plants exhibit antivenom properties (Gutiérrez et al., 2021). Worldwide, especially in rural areas, different parts of plant extracts have traditionally been used for snakebite treatment alone or in combination. The ethnomedicinal studies reported that around 116 plants, including several trees, herbs, shrubs, climbers, bulbs, and ferns, have snake antivenom potential. Thus, in this review article, we have enumerated some ethnomedicinal plants possessing snake antivenom potential and elucidated their phytoconstituents and mechanisms of action for snakebite treatment.

2 Venomous snake

Among 3,848 snakes found worldwide, around 750 are venomous (Uetz et al., 2020). Particularly in India four species *Bungarus caeruleus* (common krait), *Naja naja* (spectacled cobra), *Echis carinatus* (saw-scaled viper), and *Daboia russelii* (Russell's viper) of more than 60 venomous species are the leading cause of bites and resulting morbidity (Sulabh and Shivahre, 2018; Senji Laxme et al., 2019).

2.1 Complications originated in response to snake venom

Snake venom is a complex fusion of phospholipase A2 (PLA2s), myotoxins, hemorrhagic metalloproteinases, other proteolytic enzymes, coagulants, cardiotoxins, cytotoxins and neurotoxins, enzymes, and toxic proteins (Soares et al., 2004). Snake envenomation can have various clinical consequences, such as systemic and local pathology. Serious problems can arise from snakebite complications; in the cases of viper bites, the majority of patients (17/24) were diagnosed with intracranial hemorrhage and ischemic stroke, and in some instances, there may be cerebral complications also (Huang et al., 2022). Similarly, *Echis carinatus* envenomation results in necrosis, hemorrhage, blistering, and swellings due to the occurrence of both caring and other metalloproteases in the snake venom (Jayawardana et al., 2018), whereas *Naja nigricollis* envenoming results in local necrosis, complement depletion, hemorrhage, and respiratory arrest or paralysis (Rivel et al., 2016). *Naja nigricollis* venom consists of cardiotoxin and phospholipase A2s (an anticoagulant enzyme that binds to coagulation factor Xa and inhibits the prothrombinase complex).

In some cases, anterior uveitis and corneal ulceration may result from poisoning. Envenomation of *Bothrops venom* in humans causes damage to local tissues, edema, hemorrhage, myonecrosis, and proteolysis. Due to multiple snake envenomation, muscle necrosis is a significant local consequence, often leading to irreversible tissue loss (Rucavado et al., 2005; Bittenbinder et al., 2024). In addition, as a result of vessel degeneration and hemorrhagic metalloproteases-induced ischemia, myonecrosis can evolve as an indirect action or a direct effect of myotoxic homologous PLA2s on muscle cell plasma membranes (Gutierrez et al., 2009). It is also reported that the venom's composition determines the type of problems, which differs by geographic location (Narvencar et al., 2022).

2.2 Limitations of antisnake venom therapy

The only reliable treatment available against snake venom poisoning is antivenom immunotherapy. However, several side effects, such as pyrogen reaction, serum sickness, and anaphylactic shock, are associated with this antivenom immunotherapy. Such symptoms can mainly arise due to the action of highly concentrated non-immunoglobulin proteins in commercially existing hyperimmune antivenoms (Makhija and Khamar, 2010). However, intravenous antivenom administration prepared from the Immunoglobulin G(IgG) of sheep or horses has been used as the most effective remedy for systemic envenoming of victims. The clinical limitation of snake poisoning treatment with antivenom is the lag time in response to the effect of envenomation, which develops rapidly after a bite. Consequences of such envenomation include extreme pain, necrosis, edema, and localized hemorrhage; this leads to deformity and lifelong scarring (Makhija and Khamar, 2010). Specially antivenoms manufactured in India are only against the four main venomous snake species (*D. russelii*, *B. caeruleus*, *Naja naja, and E. carinatus*) and are not able to neutralize the venom of some species (Senji Laxme et al., 2019). In addition to a better quality antivenom, there is also a need for better training of doctors in snakebite management, thus reducing mortality (Simpson, 2008).

3 Ethnobotanical for the treatment of snakebite

As ethnobotanicals are inexpensive and easily accessible, they are widely used by indigenous people for snakebite treatment (Gomes et al., 2010). In rural areas, herbal medicine without antivenom therapy against envenomation is generally accepted among ethnic groups. Plant extracts provide an extraordinarily rich source of pharmacologically active bioactive metabolites and have numerous pharmacological properties. Interaction of such metabolites with toxins or enzymes neutralizes and inhibits their activities (Adrião Asenate et al., 2022). So, plant-based remedies are significant for snakebite treatment and can find suitable alternatives to antivenom immune therapy. Venomous snakes are found in almost all parts of the world; many plant materials are used as

Abbreviations: BthTX1, Bothropstoxin-1; BthTX2, Bothropstoxin-2; ELISA, Eenzyme Linked Immunosorbent Assay; IgG, Immunoglobulin G; PLA2, Phospholipase A2; RIA, Radioimmunoassay; WHO, World Health Organisation.

traditional medicine for snakebite treatment (Hussain and Kingsley, 2024). Generally, an aqueous extract of methanol and ethanol from plants is prepared for medical application. Plant extract of medicinal value is administered via different routes, for example, the topical solution applied to the snakebitten area, ingestion of the decoctions plant extract, chewing leaves, and barks, etc. snakewise uses of traditional herbs, their plant extract, and ad method of administration are reviewed by David et al., 2022.

Since ancient times, the plant roots of *Ophiorrhiza mungo*, *Gymnema sylvestre*, *Peristrophe bicalyculata*, *Cucumis colosynthis*, *Gloriosa Superba*, *Alangiumsi salvifolium*, *Enicostemma axillare*, and *Aristolochia indica* leaves have been used in ayurvedic medicine. According to the Ayurveda system, specific plant species may be used against specific snakebites, e.g., In the treatment of krait bite, *Abrus precatorius* root extracts have been used; Azadirachta indica leaf paste is used against viper bites in addition to rock salt (Shukla et al., 2010). Casearia sylvestris bark and leaves have been used as an ideal ayurvedic medicine for snakebite treatment in the Columbia and Indian subcontinents for a long time.

Knowles (1921), published the first plant-based antidote. He screened some phytoconstituents from plants used by traditional healers. Still, unfortunately, he failed to define their efficacy against snake envenomation due to the sublethal or non-lethal dosage of venom. Further, 314 plants and 184 combinations were screened for lethality, ignoring the systemic changes caused by snake venom and advocating the efficacies of herbal antidotes (Mhaskar and Caius, 1931). It has been investigated that *N. naja* venom is neutralized, and the hemorrhage effect due to *Vipera russelli* and *Trimeresurus flavoviridis* venoms are further reduced by *Aristolochia species* ether soluble plant substances (Vishwanath et al., 1987). In mice, rhizomes of *Curcuma* species inactivated the postsynaptic neurotoxin of Thai kobra (*N. naja* siamensis) (Ratanabanangkoon et al., 1993). *S. magnificum bark*, *Mucuna pruriens var.* utilis, *Strophanthus gratus*, and *S. hispidus* leaves aqueous extract increases the clotting time with a standardized dose of *E. carinatus* snake venom (Houghton and Skari, 1994). Compared to the other group of mice treated with *E. carinatus* and *N. nigricollis* snake venom, the survival period of male albino mice was increased by the application of Guiera senegalensis leaf extracts (Abubakar et al., 2000; Otero et al., 2000 have reported that stem bark extract of *Tabebuia rosea, Brownea rosademonte, Trichomanes elegans whole plants, Heliconia curtispatha* rhizomes, and *Bixa orellana, Gozalagunia panamensis, Struthanthus orbicularis, Philodendron tripartitum* branches and leaves and the ripe fruit of Citrus lemon, leaves, stems and branches of Ficus nymphaeipholia inhibited the hemorrhage (Otero et al., 2000).

In addition (Otero et al., 2000), have reported that plant extracts of *Aristolochia grandiflora, Columnea kalbereyeriana, Sida acuta, Selaginella* sp rhizomes of *Renealmia alpinia*, the stem of *Strychnos xynguensisleaves*, branches of *Hyptis capitata, Ipomoea cairica, Ocimum micranthum, Piper pulchrum, Neurolaena lobata Castilla elastica, Siparuna thecaphora, Allamanda cathartica, Capsicum frutescens* macerated fruits, unripe fruit of *Crescencia cujete*, branches and leaves of *Passiflora quadrangularis* and *Piper arboretum* partially inhibited hemorrhage caused by snake venom. Aguiyi et al., 2001 have recorded that *M. pruriens* var. utilis seeds aqueous extract inhibits venom-induced mycotoxin, cytotoxic coagulation in experimental animals caused by *E. carinatus* snake.

Alcoholic and aqueous extracts of dried roots of *Mimosa pudica* inhibit myotoxicity and lethal effects induced by toxic enzymes of *Naja kaouthia* venom (Mahanta and Mukherjee, 2001). *M. pudica* also possesses anti-hyaluronidase activity against *N. naja*, *V. russelii*, and *E. carinatus* venom (Girish et al., 2004). Furthermore, the butanol extract of *M. pudica* and *Eclipta prostrata* showed therapeutic significance, as it partially inhibits phospholipase A2 and hemorrhage induced by the proteolytic activity of Malayan pit viper venom (Pithayanukul et al., 2004). Oral administration of garlic was used as a prophylactic alternative for cobra venom-induced histochemical patterns and histological changes of the hepatic and gastric tissues in the rats (Rhamy and Hemmaid, 2001). A water-methanol extract from stems of Parkia biglobosa can neutralize *N. nigricollis* and *E. ocellatus* snake venom in some experimental models (Asuzu and Harvey, 2003). Partial inhibitions of *Bothrops* and *Crotalus durissus terrificus* venoms' phospholipase function were shown by crude aqueous extract from *Mandevilla velutina* (Biondo et al., 2003). The *Marsypianthes change* dry extract from the Brazilian plant inhibits fibrinogen clotting caused by the Brazilian snake venom, suggesting its role in affecting thrombin-like enzymes (Castro et al., 2003). *Casearia sylvestris* aqueous extract has shown anti-phospholipase A2 (PLA2), myotoxic, and hemorrhagic activities induced by crude snake venoms and toxins (Raslan et al., 2002). In addition, *Casearia mariquitensis* neutralizes haematological and systemic alterations caused by Bothrops neuwiedi pauloensis venom (Izidoro et al., 2003). *Mandevilla illustris* inhibited *C. durissus* terrificus snake venom phospholipase activity and increased the survival time of patients (Biondo et al., 2004). *Struthanthus orbicularis*, *B. orellana, Ficus nymphaeifolia, Gonzalagunia panamensis* branches and leaves, *T. rosea, B. rosademonte* stem and barks, *T. elegans* and *Pleopeltis percussa* whole plant, *H. curtispatha*, *R. alpinia*, and *Dracontium croatii* rhizomes and the ripened fruits of *Citrus lemon* inhibit the defibrination, edema, and coagulation caused by *Bothrops asper* venom (Nunez et al., 2004).

The ethanol root extract of *Acalypha indica L.* has a potent snake venom-neutralizing ability (Shirwaikar et al., 2004). Aqueous extract of *Tabernae montana* catheriensis prevented the lethal effect induced by *C. durissus terrificus* snake venom (de Almeida et al., 2004). It partially inhibited the myotoxic effects of *B. jararacussu* venom containing two myotoxins, bothropstoxin-1(BthTX1) and bothropstoxin-2(BthTX2), with low PLA2 activity (Veronese et al., 2005). The methanol extract of *Annona senegalensis* Pers root bark caused a decrease in the *N. nigricollis* venom-induced hyperthermia in rats (Adzu et al., 2005). *In vitro, Musa paradisiaca* L. successfully inhibited viper venom actions e (Borges et al., 2005). *Pentaclethra macroloba* exhibited complete neutralization of hemorrhagic and nucleolytic activities caused by several snake venoms and partial inhibition of myotoxic, phospholipase, lethal, and edema activities. It neutralized *Bothrops jararacussu* metalloprotease-induced hemorrhage in the *in-vivo* model (daSilva et al., 2005). Aqueous extract of *Croton urucurana* containing proanthocyanidins reduced the hemorrhagic activity of *B. jararaca* venom (Esmeraldino et al., 2005). Aqueous extract of fresh roots, leaves, and stems of *Mikania glomerata* efficiently inhibited different pharmacological, toxic, and enzymatic effects caused by venoms from *Bothrops* and *Crotalus* snakes (Maiorano et al., 2005). *Cordia Verbenaceae* neutralized paw

edema induced by *B. jararacussu* snake venom (Ticli et al., 2005). Aqueous extract of aerial parts of *Bauhinia fortification* is a source of natural inhibitors of serine proteases participating in blood clotting, disturbances induced by *Bothrops* and *Crotalus* crude venoms (Oliviera et al., 2005). The methanol bulb extract of *Crinum jagus* significantly prevented mice from hemorrhage, myonecrosis, and death induced by a lethal dose of *E. ocellatus*, *Bitis arietans*, and *N. nigricollis* venoms (Ode and Asuzu, 2006).

Tamarind seed extract inhibited the PLA2, hyaluronidase, protease, amino acid oxidase, and 5-nucleotidase enzyme (major hydrolytic enzymes) activities of *Vipera russelii* venom in a dose-dependent manner. Additionally, the extract inhibited indirect hemolysis by venom and the degradation of the human fibrinogen B-chain. The extract showed a moderate effect on clotting time. Edema, myotoxic, hemorrhage effects, and lethality caused by venom were significantly inhibited when different doses of the extract were preincubated with venom before assays. On the other hand, animals that received extract 10 min after the injection of venom recovered from toxicity caused by the venom (Ushanandini et al., 2006). Dichloromethane extract from leaves of *Artemisia campestris* inhibited the venom-induced actions of viper *Macrovipera lebetina* (Memmi et al., 2007). Ethanol extract of *Galactia glaucescens* inhibited the neuromuscular paralysis caused by *C. durissus terrificus* venom (Dal Belo et al., 2008). Edema, myonecrosis, and hemorrhage coagulation caused by Indian *E. carinatus* (saw-scaled viper) venom were inhibited by the methanol seed extract of *Vitis vinifera* L. (Mahadeswaraswamy et al., 2008). The aqueous extract of *Schizolobium parahyba* displayed potent antivenom ability (Mendes et al., 2008; Vale et al., 2008). The active fractions of *Aristolochia indica*, *G. superba*, *H. indicus*, *E. prostrata*, *Strychnos nux vomica*, and *A. paniculata* inhibited rattlesnake venom-induced actions (Samy et al., 2008). The animals that received the extract of *Aristolochia odoratissima* leaves orally were prevented against *Bothrops atrox* venom as the mortality of experimental animals reduced from 100% to 80% (Usubillaga et al., 2005). *Tabebuia aurea* decreases hemorrhagic, inflammatory, and myotoxic activities induced by the venom of *Bothrops neuwiedi* (Reis et al., 2014). Ethanolic extract of *Cordia macleodii* bark showed antivenom potential against *Naja venom* (Soni and Bodakhe, 2014). The root extract of *Ophiorrhiza mungos* showed a neutralizing effect against *D. russelii* venom (Krishnan et al., 2014). Extracts of *Euphorbia hirta* and its metabolites protect against snake venom-induced lethality (Gopi et al., 2015).

The methanol root extract of *V. negundo* Linn. and *Emblica officinalis* significantly inhibited the lethal activity induced by *V. russelii* and *N. kaouthia* venom in *in-vivo* studies; *V. russelii* venom-induced hemorrhagic, lethal, dehydrogenating, coagulant and inflammatory activity was significantly inhibited by both plant extracts (Alam and Gomes, 2003). *Hemidesmus indicus* root extracts effectively inhibited viper venom-induced lethal coagulation, hemorrhagic, and inflammatory activities (Alam et al., 1994). Active bioactive metabolites from *S. nux vomica* whole seed extract neutralized lethality, hemorrhage, defibrinogenating PLA2 induced by *D. russelii* venom and enzyme activity, and *N. kaouthia* venom-induced lethality, cardiotoxicity, neurotoxicity, PLA2 enzyme activity and it also neutralized viper venom-induced lipid peroxidation in experimental animals (Chatterjee et al., 2004). Ethanolic root extract from *Cynanchum paniculatum* also shows antivenom properties (Xiong et al., 2018).

4 Phytoconstituents with the potential to neutralize snake venom

For many years, it has been well-known that phytoconstituents of numerous plant extracts can neutralize snake venoms. Details of phytoconstituents with snake venom-neutralizing potential are given below: Acids- 2-OH-4 methoxy benzoic acid from *H. indicus* possesses viper venom-induced potent antipyretic and anti-inflammatory properties. It has been investigated that functional groups of these metabolites, particularly hydroxy and methoxy, were partly responsible for neutralizing the hemorrhagic activity and lethal effect of *Vipera russelii* venom (Alam and Gomes, 1998a). The venoms of Indian common snake *V. russelii, N. kaouthia, E. carinatus*, and *Ophiphagus hannah* hemorrhagic, lethal and defibrinogenic action has been neutralized with four metabolites, *Pimpinella anisum* anisic acid, *H. indicus* 2-hydroxy-4-methoxy benzoic acid, *Filipendula ulmaria* salicylic acid and *Salix alba* aspirin in experimental animals. The lethal effect of these snake venoms was neutralized effectively *in vivo* and *in vitro* with anisic acid and 2-hydroxy-4-methoxy benzoic acid. In addition, salicylic acid has effectively neutralized Viper and Echis venom-induced hemorrhagic activity (Alam and Gomes, 1998b). Rosmarinic acid from *Cordia verbenaceae* possesses phospholipase A2 inhibitor activity, and it has been reported as a new antidote against snake *B. jararacussu* venom (Binorkar and Jani, 2012).

Alkaloids- Atropine, in particular members of the Solanaceae family, has an inhibitory function against *Dendroaspis angusticeps* and *D. polyposis* venom. These venoms release neurotransmitters at the cholinergic nerve terminals, so it is believed that a cholinergic blocker such as atropine decreases their effects. PLA2 Inhibitor isolated from A. indica methanolic leaf extract neutralizes *R. viper*, *N. naja*, and *N. kaouthia* phospholipase A2 enzymes function in a dose-dependent manner (Mukherjee et al., 2008).

Coumestans and steroids- Beta-sitosterol and stigmasterol isolated from *Pluchea indica* root extract effectively inhibited Viper and cobra venom (Gomes et al., 2007). Beta-sitosterol and stigmasterol have inhibited Venom-induced changes in superoxide dismutase and lipid peroxidation activity. When administered to animals and humans and in *in-vitro* tests, sitosterol shows many pharmacological properties, including anti-inflammatory ability. The capacity of steroids for complex formation has been known in many cases. The physiological importance of these steroids lies in their ability to convert fats and fatty acids into water-soluble or emulsifiable metabolites and thus facilitate intestinal absorption.

Molecules of an extended shape carrying a hydrophilic group at one end can associate with hydrophobic ones surrounding them. The hydrophilic groups turned to the outside and formed molecular complexes with their physicochemical properties. Cholesterol is an occasionally occurring component in plants and has been identified in snake venom antibodies, like onion skins and the root of *Ehretia buxifolia* Roxb. In the early 1900s, cholesterol's capacity for complex formation became evident, and it was observed that adding cholesterol destroys the violent hemolytic activity of the saponin

digitonin. This property of cholesterol explains how cholesterol combines with some of the plasma proteins and interacts with proteins in cell membranes (Yeagle, 1985). Hemolysis is one of the many consequences of the action of snake venoms, phospholipases being the responsible enzymes. These esterases act on the serum lecithin, splitting off the hemolytic lysolecithin. It has been found that cholesterol combines in equimolecular proportion with lysolecithin, the product being devoid of hemolytic activity. Wedelolactone, a coumestan contained in *E. prostrated* L., was reported to be an active metabolite in fighting against snake venoms (Wagner et al., 1986). Wedelolactone, stigmasterol, and sitosterol inhibit the effects of South American rattlesnakes (Mors et al., 1989).

Enzymes, peptides, and pigments-snake venom molecules comprise proteins and some non-protein components. These proteins can be dissolved with natural solvents like bromelain and papain. Bromelain is present in pineapple (*Ananas comosus*), while papain is found in papaya fruit (*Carica papaya*). These two naturally existing proteolytic enzymes can neutralize snake venom proteins. A peptide metabolite (6000 Da) reported anti-cardiotoxic activity against cobra venom was isolated and purified from the plant of *Schummanniophyton magnificum* (Houghton et al., 1992). Turmerin, a protein from turmeric (*Curcuma longa* L.), reported inhibiting the enzymatic activity with neutralization of the edema, cytotoxicity, and myotoxicity of multitoxic phospholipase A2 of cobra (*N. naja*) (Chethankumar and Srinivas, 2008). Melanin isolated from black tea was reported to possess antivenom potential against *Agkistrodon contortrix laticinctus*, *Agkistrodon halys blomhoffii*, and *Crotalus atrox* snake venoms (Hung et al., 2004).

Glycoprotein and glycosides-a multiform glycoprotein with functional oligosaccharides isolated from *M. pruriens* seeds neutralize *E. carinatus* venom-induced actions (Guerranti et al., 2004). A glycoprotein (WSG) isolated from *Withania somnifera* is reported to inhibit the phospholipase A2 activity of NN-Xia-PLA2 isolated from cobra venom (*N. naja*), entirely at a mole-to-mole ratio of 1:2 (NN-XIa-PLA2:WSG) (Machiah et al., 2006). It prolonged the death time and reduced the toxicity of the experimental mice approximately ten times as compared to antivenom alone. The WSG also inhibits several other PLA2 isoforms from the venom to a different extent. Hyaluronidase activity induced by cobra (*N. naja*) and viper (*D. russelii*) venoms was inhibited by WSG. It has also been reported to inhibit the hyaluronidase activity of Indian cobra (*N. naja*) venom (Girish et al., 2004; Deepa and Gowda, 2006). Salireposide and benzoylsalireposide isolated from *Symplocos racemosa* showed phosphodiesterase activity against snake venom. The methanolic extract of the stem bark of *S. magnificum* and schumanniofoside, a chromone alkaloidal glycoside, was isolated to reduce black cobra (*Naja melanoleuca*) venom-induced lethal effect in mice. The probable mechanism of this action is oxidative inactivation of the venom.

Phenols- *B. asper* venom-induced PLA2 activity was neutralized by 4- nerolidylcatechol from *Piper peltatum* and *Piper umbellatum* (Nunez et al., 2005). The ethanolic extract of seed kernels from Thai mango (*Mangifera indica* L.) and its major phenolic metabolites pentagalloyl glucopyranose show dose-dependent inhibitory effects on hyaluronidase, phospholipase A2 and L-amino oxidase of *Calloselasma rhodostoma* and *N. kaouthia* venoms in *in-vitro* studies. The anti-hemorrhagic and anti-dermo necrotic activities of seed kernel against both venoms were supported by *in-vivo* studies (Akubue, 1986). The plant polyphenols from the aqueous extracts of *Pentace burmanica*, *Pithecellobium dulce*, *Areca catechu*, and *Quercus infectoria* block nicotinic acetylcholine receptor non-selectively by precipitation of *N. kaouthia* venom (Leanpolchareanchai et al., 2009).

Pterocarpus- Cabenegrin A-1 and Cabenegrin A-2 isolated from an aqueous extract of the root of a South American Plant called Cabeca de Negra have been reported as an anti-snake oral antidote (Nirmal et al., 2008). Similarly, the extract of *Harpalyce Brasilia* Benth, a South American plant commonly called Portuguese snake herb, also yielded cabenegrin A-2 (phenolic pterocarpan in nature). Edunol, a pterocarpan isolated from *Harpalyce brasiliana* used in Brazil against snakebites and roots of *Brongniartia podalyrioides* and *Brongniartia intermedia* (Leguminosae), edunol reduced the expected death rate of mice previously administered with *B. atrox* (Nakagawa et al., 1982) venom along with antiproteolytic, antimyotoxic and PLA two inhibiting properties (Reyes–Chilpa et al., 1992).

Tannins- The tannin from persimmon fruit from *Diospyros kaki* was found to inhibit edema in mice, resulting from envenomation by sea snakes and was reported to improve the survival rate in mice (Okonogi et al., 1979). Ellagic acid, a metabolite isolated from the aqueous extract of *C. sylvestris*, has been reported to have anti-snake venom potential mainly against *Bothrops* genus (daSilva et al., 2008).

Terpenoids-glycyrrhizin, a natural triterpenoid saponin isolated from the root extract of *Glycyrrhiza glabra* (840 Da), has been identified as an inhibitory metabolite against thrombin (Francischetti et al., 1997). This metabolite is well known to possess anti-inflammatory activity, and glycyrrhizin is also reported to show *in-vivo* antithrombic properties against snake venom; it inhibits both *in vitro* and *in-vivo* venom-induced changes in hemostasis, suggesting to possess potential antiophidic activity (Assafim et al., 2006). Potassium salt of gymnemic acid, a triterpenoid glycoside isolated from *G. sylvestre* known to inhibit the ATPase activity in *N.naja* venom (Kini and Gowda, 1982). Lupeol acetate obtained from the Indian sarsaparilla *H. indicus* R.Br. could neutralize the haemorrhage, lethality, defibrinogenation, edema and PLA2 activity induced by *D. russelii* venom significantly. In experimental animals, it also neutralized *N. kaouthia* venom-induced cardiotoxicity, lethality, respiratory changes, and neurotoxicity (Chatterjee et al., 2006). *Bothrops neuwiedi* and *B. jararacussu* venom-induced fibrinogenolytic, hemorrhagic, and caseinolytic activity of class P-1 and three metalloproteases inhibited by neo-clerodane, a diterpenoid, purified from *Baccharis trimera* (Januario et al., 2004). Oleanolic acid inhibited sPLA(2) activities of *N. naja* and *V. Russell* snake venoms in a concentration-dependent manner. Prevention of *in vitro* and *in vivo* sPLA2 activity by oleanolic acid suggests the anti-inflammatory properties of some oleanolic acid-possessing medicinal plants (Dharmappa et al., 2009). The pentacyclic triterpenes are present widely in some anti-snake venom plants like *Centipede minima*, *Aegle marmelos*, *Aloe barbadensis Mill*, *Phyllanthus niruri*, *P. emblica*, *Alstonia scholaris*, *Elephantopus scaber*, etc., showed nearly 20% inhibition against snake venom (Mors et al., 2000). Quinovic acid-3-O-beta-D-fucopyranoside, Quinovic acid-3-O-alpha-rhamnopyranoside (Fatima et al., 2002), and quinovic acid-3-O-beta-D-glucopyranosyl (1-4) beta-D-fucopyranoside obtained from the ethyl acetate extract of *Bridelia ndellensis* barks, and *Mitragyna stipulosa* showed significant

neutralizing activity against snake venom phosphodiesterase −1 (Castro et al., 1999; Mostafa et al., 2006). Triterpenoid saponin isolated from *P. macroloba* neutralizes the antiproteolytic and anti-hemorrhagic actions caused by *Bothrops* snake venom. These inhibitors could neutralize the fibrin (ogen) olytic and proteolytic activities of class P-1, P-2 metalloproteases purified from *B. jararacussu* and *B. neuwiedi* venoms (daSilva et al., 2007). Ursolic acid, a common phytoconstituent of several medicinal plants, neutralizes PLA2 enzymes isolated from *N. naja* and *V.* Russell venom (Nataraju et al., 2007). Betulinic, ursolic, and oleanolic also exhibited inhibition against the enzymatic and biological effects induced by a P-I snake venom metalloproteinase (Preciadoa et al., 2018).

Quinonoid Xanthene- Ehretianone, a quinonoid xanthene purified from the root bark of *E. buxifolia*.Rox.B. has been known to have antivenom (*E. carinatus*) activity (Selvanayagam et al., 1996).

Resveratrol–Hong Bei Si Chou is an herbal remedy used to cure snakebites in *China's Guangxi province*. It was reported that resveratrol (3,4,5-trihydroxy trans-stilbene) purified from the ethyl acetate part of Hong Bei Si Chou could antagonize snake toxins in both *in-vivo* and *in-vitro* conditions (Yang et al., 1998). Alkaloid (12-methoxy-4-methylvoachalotine) extract of *Tabernaemontana catheriensis* neutralized lethality induced by *Crotalus durrissus terrificus* snake venom (Batina et al., 2000).

Other active metabolites and chemical groups-several plant phytoconstituents like flavonoids, xanthenes, polyphenols, quinonoids, and terpenoids have enzyme-inhibiting abilities, protein-binding activity, also neutralize snake venom PLA2 activities of both cobra and viper venom (Alam et al., 1996). Complete inhibition of hemorrhage was observed with the ethanol, ethyl acetate, and aqueous extract of *Bursera simaruba*, *Clusia torresii*, *C. palmana*, *Croton draco*, *Persea americana*, *Phoebe brenesii*, *Pimenta dioica*, *Sapindus saponaria*, *Smilax cuculmeca* and *Virola koschnyi* (Castro et al., 1999). Chemical profiling of these extracts indicates the presence of catequines, anthocyanins, flavones, and condensed tannins, which may be responsible for the inhibitory effect by chelation of the zinc needed for the activity of *B. asper* venoms hemorrhagic metalloproteinases. Plant-derived aristolochic acid, quercetin, indomethacin, tannic acid curcumin, and flavone exhibited inhibition, and aristolochic acid and quercetin completely neutralized the hyaluronidase activity (Pithayanukul et al., 2005). Phytoconstituents of *Andrographis paniculata* exhibited anti-phospholipase A2 activity against the venom of Russell's viper (*Daboia russellii*) (Shivashankar et al., 2019).

Further, these inhibitors decrease the local tissue damage and reduce the easy diffusion of systemic toxins, thus increasing the survival time. Medicinally important herbal metabolites (acalyphin, chlorogenic acid, stigmasterol, curcumin, and tectoridin) were screened against *Russels viper* PLA2 (Nirmal et al., 2008). These metabolites showed favorable interactions with the amino acid residues at the active site of *R. viper* PLA2, substantiating their proven anti-inflammatory and antidote efficacy. An active metabolite (SNVNF) was purified from the whole seed extract of *S. nux* vomica, which may effectively antagonize *Daboia* Russell venom-induced lethality, defibrinogenating, hemorrhage, PLA2 enzyme activities, edema, and *N. kaouthia* induced lethality, neurotoxicity, cardiotoxicity, and PLA2 enzyme activities. The hexane extract of *C. longa* rhizomes, ar-turmerone (Ferreira et al., 1992), was also reported to inhibit the proliferation of human lymphocytes' natural killer cell activity. This metabolite possesses anti-lethal activity against the venom of *Crotalus durrissimus terificus*. Moreover, when administered in mice, it showed anti-hemorrhagic activity against *B. jararacussu* venom.

5 Mechanisms of snake venom neutralization by herbal compounds

Herbal metabolites with snake venom neutralization properties usually follow three mechanisms- 1) venom following herbal metabolites, 2) venom and herbal components in combination, and 3) herbal metabolites following venom. Among these, the third one is close to clinical conditions. One of the key elements for the herbal metabolites to demonstrate their neutralizing actions is the amount of venom. Venom quantity is inversely proportional to the neutralizing effects of herbal metabolites of any plant. So, the venom dose should be tried from a lower to a higher dose. Many hypotheses have been proposed as (1) protein precipitation hypothesis (Vale et al., 2008), (2) enzyme inactivation hypothesis (Hung et al., 2004), (3) chelation hypothesis (Castro et al., 1999), (4) adjuvant activation hypothesis (Alam and Gomes, 1998c), (5) anti-oxidant hypothesis (Chatterjee et al., 2006), (6) protein folding hypothesis, (7) combination hypothesis (Alam and Gomes, 1998a) and many more. The hypothesis mentioned above has its limitations. Among these, the protein-precipitation-inactivation hypothesis is more acceptable. However, more emphasis should be focused on this area soon.

6 Benefits and limitations of plant-based remedies

It has been well established that ethnomedicinal plants are pharmacologically efficient against snake venom. The importance of phytochemical compounds obtained from these plants in inhibiting the activity of phospholipase A2, an enzyme frequently present in snake venoms, is highlighted in a study published in the Journal of Pharmacognosy and Phytochemistry (Kankara et al., 2020). Certain ethnomedicinal plants have been shown to prevent snake venom in research studies effectively reported using albino rats. This research finding scientifically justifies the traditional use of these ethnomedicinal plants (Sani et al., 2020). In addition to their ability to neutralize venom, ethnomedical herbs have shown promise in repairing the specific tissue damage caused by snakebites. This implies that the therapeutic potential of these plants is multifaceted and extends beyond the capabilities of conventional antivenoms (Félix-Silva et al., 2017). The usual method for treating snakebites is still traditional antivenom therapies, although ethnomedicinal plants provide a useful alternative. Ethnomedicinal plants are important resources with a wide range of pharmacological properties that make them more accessible and affordable than traditional antivenoms, particularly in areas with limited resources (Deshpande et al., 2022).

Comprehensive scientific research on ethnomedicinal plants demonstrating their efficacy as snakebite antivenom is limited (David Paul Raj et al., 2022). Moreover, the intricate composition

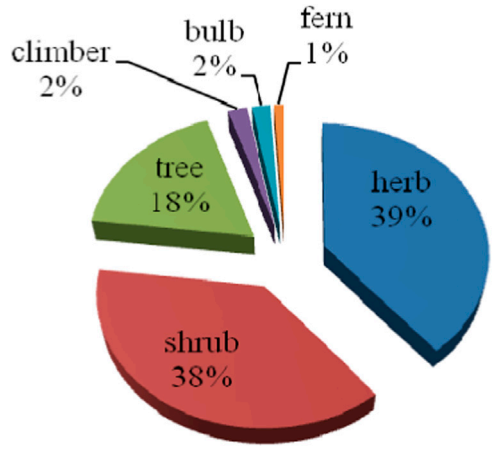

FIGURE 1
Nature of medicinal plants used in snakebite treatment.

of snake venom and its wide-ranging impact on the body make it difficult to create a universally potent antivenom derived from plants. Furthermore, the complex makeup of snake venom and its extensive effects on the body make it challenging to develop a plant-based antivenom for different snake species (Liaqat et al., 2022; Patricia et al., 2022). New treatments are being investigated due to the existing antivenoms' restricted use and stringent storage restrictions. Despite this, there is still an important gap in the literature regarding these herbal remedies' phytochemical composition and safety evaluations (Mokua et al., 2021). Moreover, producing and using plant-based antivenoms is challenging without empirical validation (Omara et al., 2021).

7 Future of antivenom and herbal therapy and nanotechnology

Considering the limitations of snake antivenom (Gomes et al., 2010), the world is looking for an alternative to snakebite treatment. Still, no suitable alternative measures, except natural herbal remedies, attract researchers due to their snake antivenom potential. These herbal medicines might be an alternative to cure snake envenomation since they are inexpensive, readily available, stable at room temperature, and can neutralize snake venom components. In the present scenario, the future of snake antivenom lies in herbal compounds, and a combination of these antidotes may be proven as a suitable alternative to snakebites shortly. Combination therapy is a traditional practice of the Ayurvedic system. There are various commercially available therapeutic and ayurvedic medicines, e.g., Articulin-F, which comprises the fixed combination of *C. longa*, *W. somnifera*, *Boswellia serrata*, and zinc for treating osteoarthritis. Trikatu is comprised of long pepper, black pepper, and ginger to treat digestive disorders. In Ayurveda, more than twenty formulations are available, which use a combination of herbal metabolites, metal ions, and spices for practical use. According to Ayurveda, a medicinal plant may need to be administered with other plants to exert its therapeutic effects. The second plant may stimulate the action of the first, whereas the third might help prevent the second plant's toxicity.

Nanotechnology is an emerging field of science that has revolutionized the progress in chemical, physical, and biological sciences through its applications in biomedical research. Nanotechnology is also contributing to the field of herbal anti-snake venom research. Medication delivery, better stability, reduced toxicity, bioavailability, and targeted drug delivery are all possible benefits of nanotechnology in herbal anti-snake venom. Thus, nanotechnology directly impacts human health and the environment by contributing to the era of biomedical sciences. Due to the miniature size of nanoparticles, these particles can efficiently translocate to their target site through bloodstreams or their entry portals. Antisnake venom herbal metabolites conjugated with nanoparticles are now an expanding area of present-day research. 2-hydroxy-4-methoxy-benzoic acid (HMBA) purified from the root extract of Indian sarsaparilla (*H. indicus*), conjugated with gold nanoparticle when administered, is found to increase the viper venom neutralizing efficacy of HMBA and decreased the toxicity (Saha and Gomes, 2017). Saha et al. have synthesized gold nanoparticles using gold salt, exploiting the reducing property of *Vitex negundo*, and assessed its potentiality against viper venom-induced acute stress and acute cytokine response in the experimental animal model (Saha et al., 2015). This nanoparticle reached the snake venom target sites and neutralized the deleterious venom's effects on the major organs, including the kidney and liver.

The anti-inflammatory and anti-oxidant potential of curcumin, isolated from *C. longa*, has been reported well (Menon and Sudheer, 2007). When conjugated with gold nanoparticles by the absorption method, curcumin is administered, followed by an assessment of its ant-viper venom activity in the experimental animal model. It neutralizes local damages (Ghosh and Gomes, 2016). It was suggested that curcumin-conjugated gold nanoparticles might act by neutralizing viper venom-induced local damages by inhibiting the pro-oxidant activity of the venom, by direct inhibition at the enzymatic level, and by interfering with cellular markers, including inflammatory markers and anti-oxidants (Ghosh and Gomes, 2016). In *ex-vivo* and *in vitro* research, Oliveira et al. (2019) demonstrated the neutralization of silver nanoparticles against *B. jararacussu* snake venom-induced neurotoxicity and myotoxicity (Soares et al., 2018) have produced an antidote using chitosan polymer against *Bothrops jararaca* and *Bothrops erythromelas* snake venom. They have shown that chitosan polymer nanoparticles have the potential to exhibit immunoadjuvant properties. Nanoparticles have another advantage due to their pharmacokinetics and protein-binding properties, making them a low-cost and readily available alternative for antivenom against snake venom toxins. Cellular signaling molecules, enzymes, cytokines, and pro-inflammatory indicators are the molecular targets for these herb-nano-conjugated biomolecules. However, more profound and thorough research is needed to validate these herbs-nano-conjugates' actions for their approval as an effective alternative antidote against Snakebite (Gomes et al., 2018).

7.1 Detection of snake venoms, toxins, and venom antibodies

It might be difficult for victims to determine the snake species that bitten them, and clinical symptoms alone are insufficient to implement an

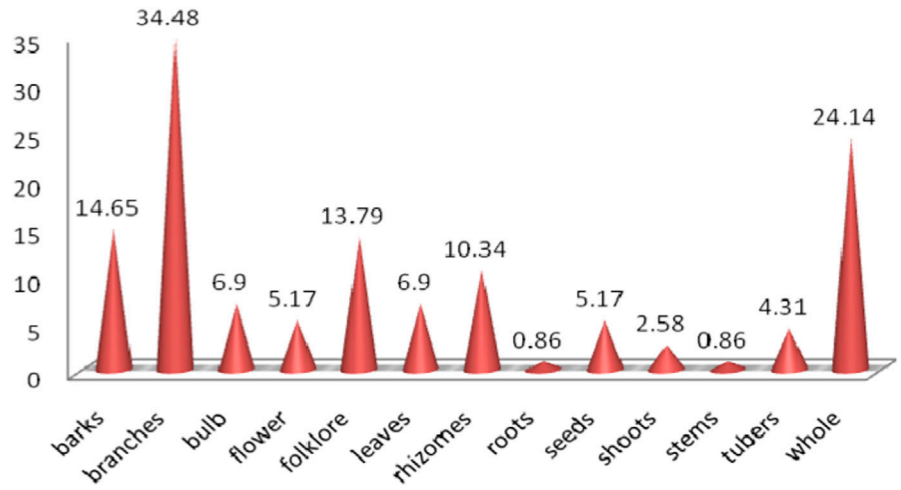

FIGURE 2
Percentage of medicinal plant parts used in snakebite treatment.

effective treatment strategy. In controlling snake envenomation, the quick or immediate identification of snake venom, including toxin antibodies in bodily fluids, is important. Instantaneous or within short-duration detection of snake venom and venom antibodies in body fluids has a significant role in managing snake envenomation. Bioassays for venom detection have been developed, including immunodiffusion, immunofluorescence, immunoelectrophoresis, haemagglutination, enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA), among others. So far, ELISA has been extensively used for venom detection and estimation. Snake species diagnosis is challenging because many venomous species are present within the same geographical region, and venom antigen cross-reaction dilutes the results. Lack of specific immunoreagents, lengthy incubation steps, low-level sensitivity, and the need for expensive equipment have restricted the widespread use of routine diagnostic methods such as RIA and ELISA during early 1980. However, significant progress has been made during the last decade to develop species-specific ELISA to detect venom toxins worldwide, particularly in developing countries where snakebite is a major medical and social issue. Species-specific immunoreagents for clinical use have been developed using hybridoma technology and affinity chromatography.

8 Statistical study

This review aims to gather and organize information on ethnomedicinal plants and their phytoconstituents used for snakebite treatment from various literature sources. Data have represented the plant types, family and parts used, phytoconstituents, etc. This review identifies 116 plant species from 59 families capable of alleviating snakebite. As a result, 39% of herbs, 38% of shrubs, 18% of trees, 2% climbers, 2% bulbs, and 1% of ferns plants have been identified to possess snake antivenom potential (Figure 1). Among these different types of plants, roots (14.65%), leaves (34.48%), rhizomes (6.90%), seeds (5.17%), branches (13.79%), barks (6.90%), stem (10.34%), tuber (0.86%), shoots (5.17%), flower (2.58%), bulb (0.86%), folklore (4.31%) and 28 (24.14%) plants are being used as a whole (Figure 2).

9 Conclusion

The most commonly used therapeutic agent for snakebite treatment is the antiophidic serum (antivenom), which is conventionally prepared by injecting a non-lethal dosage of snake venom in mammals like a goat, rabbits, and the horse, is painful for animals and uneconomic. As an alternate option, plants have been used as valuable sources for snakebite treatment because they contain many chemical compounds that can inhibit snake venom toxins. These reviews aimed to give a more thorough understanding of natural inhibitors extracted from plants and used to combat snake venoms and toxins. Additionally, these reviews aimed to enhance our understanding of possible alternatives for snakebite treatment. As reported in this review, the large, diverse, pharmacologically active molecules in medicinal plant extracts make them an attractive candidate for the future discovery of snake antivenom compounds for snakebite treatment. Nevertheless, an adequate understanding of snake-venom neutralization mechanisms requires understanding the structure and chemical nature of snake venom and plant metabolites. Interactions between snake venoms and some plant constituents have been described. However, candidate molecules responsible for snake venom neutralization and their mechanism function have yet to be characterized and explained in many plant species. These findings need additional investigation in animal preclinical trials to ensure future human clinical applications. In conclusion, this review has confirmed the ethnomedical use of 116 medicinal plants for treating snakebite victims. Besides, a more comprehensive analysis is required to validate the effectiveness of plant bioactive substances and their mechanism against snake venoms of different geographical origins and to develop nano-herbal- conjugates to save thousands of human deaths every year worldwide.

Author contributions

AK: Conceptualization, Visualization, Writing–original draft, Writing–review and editing. RB: Data curation, Validation, Writing–review and editing. RA: Writing–review and editing. JK: Writing–review and editing. PB: Formal Analysis, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1548929/full#supplementary-material

References

Abubakar, M. S., Sule, M. I., Pateh, U. U., Abdurahman, E. M., Haruna, A. K., and Jahun, B. M. (2000). *In vitro* snake venom detoxifying action of the leaf extract of *Guiera senegalensis*. *J. Ethnopharmacol.* 69 (3), 253–257. doi:10.1016/s0378-8741(99)00128-2

Adrião Asenate, A. X., dos Santos, A. O., de Lima Emilly, J. S. P., Maciel, J. B., Paz Weider, H. P., da Silva Felipe, M. A., et al. (2022). Plant-derived toxin inhibitors as potential candidates to complement antivenom treatment in snakebite envenomations. *Front. Immunol.* 13, 842576. doi:10.3389/fimmu.2022.842576

Adzu, B., Abubakar, M. S., Izebe, K. S., Akumka, D. D., and Gamaniel, K. S. (2005). Effect of *Annona senegalensis* root bark extract *Naja nigricotlis nigricotlis* venom in rats. *J. Ethnopharmacol.* 96 (3), 507–513. doi:10.1016/j.jep.2004.09.055

Aguiyi, J. C., Pagani, R., and Marinello, E. (2001). Blood chemistry of rats pretreated with *Mucuna pruriens* seed aqueous extract MP101UJ after *Echis carinatus* venom challenge. *Phytotherapy Res.* 15 (8), 712–714. doi:10.1002/ptr.913

Akubue, P. I. (1986). Schumanniofoside, the antisnake venom principle from the stem bark of *Schumanniohyton magnificum* Harms. *J. Ethnopharmacol.* 18 (2), 167–172. doi:10.1016/0378-8741(86)90028-0

Alam, M. I., Auddy, B., and Gomes, A. (1994). Isolation, purification, and partial characterization of venom inhibiting factor from the root extract of the Indian medicinal plant sarsaparilla (*Hemidesmus indicus* R.Br.). *Toxicon* 32 (12), 1551–1557. doi:10.1016/0041-0101(94)90314-x

Alam, M. I., Auddy, B., and Gomes, A. (1996). Viper venom neutralization by Indian medicinal plant (*Hemidesmus indicus* and *Pluchea indica*) root extracts. *Phytotherapy Res.* 10 (1), 58–61. doi:10.1002/(sici)1099-1573(199602)10:1<58::aid-ptr775>3.0.co;2-f

Alam, M. I., and Gomes, A. (1998a). An experimental study on evaluation of chemical antagonists induced snake venom neutralization. *Indian J. Med. Res.* 107, 142–146.

Alam, M. I., and Gomes, A. (1998b). Viper venom-induced inflammation and inhibition of free radical formation by pure compound (2-Hydroxy-4-methoxy benzoic acid) isolated and purified from anantamul (*Hemidesmus indicus* R.Br.) root extract. *Toxicon* 36 (1), 207–215. doi:10.1016/s0041-0101(97)00070-6

Alam, M. I., and Gomes, A. (1998c). Adjuvan effect and antiserum action potentiation by a (herbal) compound 2-hydroxy-4-methoxy benzoic acid isolated from the root extract of the Indian medicinal plant Sarsaparilla (*Hemidesmus indicus* R.Br). *Toxicon* 36 (10), 1423–1431. doi:10.1016/s0041-0101(98)00076-2

Alam, M. I., and Gomes, A. (2003). Snake venom neutralization by Indian medicinal plants (*Vitex negundo* and *Emblica officinalis*) root extracts. *J. Ethnopharmacol.* 86 (1), 75–80. doi:10.1016/s0378-8741(03)00049-7

Assafim, M., Ferreira, M. S., Frattani, F. S., Guimaraes, J. A., Monteiro, R. Q., and Zingali, R. B. (2006). Counteracting effect of glycyrrhizin on the hemostatic abnormalities induced by *Bothrops jararaca* snake venom. *Br. J. Pharmacol.* 148 (6), 807–813. doi:10.1038/sj.bjp.0706786

Asuzu, I. U., and Harvey, A. L. (2003). The antisnake venom activities of *Parkia biglobosa* (Mimosaceae) stem bark extract. *Toxicon* 42 (7), 763–768. doi:10.1016/j.toxicon.2003.10.004

Batina, F., Mde, F., Cintra, A. C., Veronese, E. L., Lavrador, M. A., Giglio, J. R., et al. (2000). Inhibition of the lethal and myotoxic activities of *Crotallus durissus* terrificus venom by *Taberenaemontana catherinensis;* Identification of one of the active components. *Planta Medica* 66 (5), 424–428. doi:10.1055/s-2000-8577

Binorkar, S. V., and Jani, D. K. (2012). Profile of Medicinal plants with anti-ophidian property. *J. Pharm. Sci. Innovation* 1 (5), 13–20.

Biondo, R., Pereira, M., Marcussi, S., Pereira, P. S., Franca, S. C., and Soares, A. M. (2003). Inhibition of enzymatic and pharmacological activities of some snake venoms and toxins by *Mendevilla velutina* (Apocynaceae) aqueous extract. *Biochimie* 85 (10), 1017–1025. doi:10.1016/s0300-9084(03)00138-x

Biondo, R., Soares, A. M., Bertoni, B. W., Franca, S. C., and Periera, A. M. (2004). Direct organogenesis of *Mandevilla illustris* (Vell) Woodson and effects of its aqueous extract on the enzymatic and toxic activities of *Crotalus durrissus* terrificus snake venom. *Plant Cell Rep.* 22 (8), 549–552. doi:10.1007/s00299-003-0722-6

Bittenbinder, M. A., van Thiel, J., Cardoso, F. C., Casewell, N. R., Gutiérrez, J. M., Kool, J., et al. (2024). Tissue damaging toxins in snake venoms: mechanisms of action, pathophysiology and treatment strategies. *Commun. Biol.* 7, 358. doi:10.1038/s42003-024-06019-6

Borges, M. H., Alves, D. L. F., Raslan, D. S., Pilo-veleso, D., Rodrigues, V. M., eburgo, M. I., et al. (2005). Neutralizing properties of *Musa paradisiaca* L. (Musaceae) juice on Phospholipase A2, myotoxic, hemorrhagic and lethal activities of crotalidae venoms. *J. Ethnopharmacol.* 98 (1-2), 21–29. doi:10.1016/j.jep.2004.12.014

Castro, K. N., Carvalho, A. L., Almeida, A. P., Oliviera, D. B., Borba, H. R., Costa, H. H., et al. (2003). Preliminary *in vitro* studies on the *Marsypianthes chamaedrys* (boiacaa) extract at fibrinocotting induced by snake venoms. *Toxicon* 41, 929–932. doi:10.1016/s0041-0101(03)00087-4

Castro, O., Gutierrez, J. M., Barrios, M., Castro, I., Romero, M., and Umana, E. (1999). Neutralization of the hemorrhagic effect induced by *Bothrops asper* (Serpentes: Viperadae) venom with tropical plant extracts. *Rev. Biol. Trop.* 47 (3), 605–616. doi:10.15517/rbt.v47i3.19215

Chatterjee, I., Chakravarthy, A. K., and Gomes, A. (2006). *Daboia russeli* and *Naja Kaouthia* venom neutralization by lupeol acetate isolated from the root extract of Indian sarsaparilla *Hemidesmus indicus* R. *Br. J. Ethnopharmacol.* 106 (1), 38–43.

Chatterjee, I., Chakravarty, A. K., and Gomes, A. (2004). Antisnake venom activity of ethanolic seed extract of *Strychnos nux vomica* Linn. *Indian J. Exp. Biol.* 42 (5), 468–475.

Chethankumar, M., and Srinivas, L. (2008). New biological activity against phospholipase A2 by Turmerin, a protein from *Curcuma longa* L. *Biol. Chem.* 389 (3), 299–303. doi:10.1515/BC.2008.024

Dal Belo, C. A., Colares, A. V., Leite, G. B., Ticli, F. K., Sampaio, S. V., Cintra, A. C., et al. (2008). PAntineurotoxic activity of Galactia glaucescens against Crotalus durissus terrificus venom. *Fitoterapia* 79 (5), 378–80. doi:10.1016/j.fitote.2008.04.003

daSilva, J. O., Coppede, J. S., Frnandes, V. C., Santana, C. D., Ticli, F. K., Mazzi, M. V., et al. (2005). Anti-hemorrhagic, antinucleolytic, and other antiophidian properties of the aqueous extract from *Pentaclethra macroloba*. *Journal of Ethnopharmacology* 100, 145–152.

daSilva, J. O., Fernandes, R. S., Ticli, F. K., Oliviera, C. Z., Mazzi, M. V., Franco, J. J., et al. (2007). Triterpenoid saponins, new metalloprotease snake venom inhibitors isolated from Pentaclethra macroloba. *Toxicon 50* 50, 283–291. doi:10.1016/j.toxicon.2007.03.024

daSilva, S. L., Calgarrot, A. K., Chaar, J. S., and Marangoni, S. (2008). Isolation and characterization of ellagic acid derivatives isolated from *Casearia sylvestris* S.W. aqueous extract with anti-PLA2 activity. *Toxicon* 52 (6), 655–666. doi:10.1016/j.toxicon.2008.07.011

David, P. R., Mathew, R. S., Jesse Joel, A. A., Beena Kanimozhi, T. R., and Agnes Preethy, H. (2022). Herbs as antidote for snake bite treatment- traditional practices and its future prospects- A review. *J. Nat. Remedies* 22 (3), 269–290. doi:10.18311/jnr/2022/28405

David Paul Raj, R. S., Mathew, A. A., Jesse, T., Joel, R., and Agnes Preethy, H. (2022). Herbs as antidote for snake bite treatment-traditional practices and its future prospects-a review. *J. Nat. Remedies* 22 (3), 269–290. doi:10.18311/jnr/2022/28405

de Almeida, L., Cintra, A. C., Veronese, E. L., Nomizo, A., Franco, J. J., Arantes, E. C., et al. (2004). Anticrotalic and antitumoral activities of gel filtration fractions of aqueous extract from Tabernaemontana catharinensis (Apocynaceae). *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* 137, 19–27. doi:10.1016/j.cca.2003.10.012

Deepa, M., and Gowda, T. V. (2006). Purification of a post-synaptic neurotoxic Phospholipase A2 from *Naja naja* venom and its inhibition by a glycoprotein from *Withania somnifera*. *Biochimie* 88 (6), 701–710.

Deshpande, A. M., Sastry, K. V., and Bhise, S. B. (2022). A contemporary exploration of traditional Indian snake envenomation therapies. *Trop. Med. Infect. Dis.* 7 (6), 108. doi:10.3390/tropicalmed7060108

Dharmappa, K. K., Kumar, R. V., Nataraju, A., Mohamed, R., Shivaprasad, H. P., and Vishwanath, B. S. (2009). Anti-inflammatory activity of oleanolic acid by inhibition of secretory Phospholipase A2. *Planta Medica* 75 (3), 211–215. doi:10.1055/s-0028-1088374

Esmeraldino, L. E., Souza, A. M., and Sampaio, S. V. (2005). Evaluation of aqueous extract of *Croton urucurana* Baillon (Euphorbiaceae) on the hemorrhagic activity induced by the venom of *Bothrops jararaca*, using new techniques to quantify hemorrhagic activity in rat skin. *Phytomedicine* 12 (8), 570–576. doi:10.1016/j.phymed.2004.01.012

Fatima, N., Tapondjou, L. A., Lontsi, D., Sondengam, B. L., Choudhry, M. I., and Choudhary, M. I. (2002). Quinovic acid gycosides from *Mitragyna stipulosa* first examples of natural inhibitors of snake venom phosphodiesterase 1. *Nat. Product. Lett.* 16 (6), 389–393. doi:10.1080/10575630290033169

Félix-Silva, J., Silva-Junior, A. A., Zucolotto, S. M., and Fernandes-Pedrosa, M. D. F. (2017). Medicinal plants for the treatment of local tissue damage induced by snake venoms: an overview from traditional use to pharmacological evidence. *Evidence-Based Complementary Altern. Med.* 2017, 5748256. doi:10.1155/2017/5748256

Ferreira, L. A., Henriques, O. B., Andreoni, A. A., Vital, G. R., Campos, M. M., Habermehl, G. G., et al. (1992). Antivenom and biological effects of ar-turmerone isolated from *Curcuma longa* (Zingiberaceae). *Toxicon* 30 (12), 1211–1218. doi:10.1016/0041-0101(92)90437-a

Francischetti, I. M., Monteiro, R. Q., and Guimarães, J. A. (1997). Identification of glycyrrhizin as a thrombin inhibito. *Biochem Biophys Res Commun* 237 (1), 203. doi:10.1006/bbrc.1997.6735

Ghosh, S., and Gomes, A. (2016). Russel's viper (*Daboia russeli russeli*) venom toxicity neutralizing efficacy of curcumin-gold nanoparticle (C-GNP) in an experimental animal model. *J. Toxins* 3 (2), 6.

Girish, K. S., Mohanakumari, H. P., Nagaraju, S., Vishwanath, B. S., and Kemparaju, K. (2004). Hyalurinodase and protease activities from Indian snakes venoms; neutralization by *Mimosa pudica* root extract. *Fitoterapia* 75 (3-4), 378–380. doi:10.1016/j.fitote.2004.01.006

Gomes, A., Das, R., Sarkhel, S., Mishra, R., Mukherjee, S., Bhattacharya, S., et al. (2010). Herbs and herbal constituents active against snake bite. *Indian J. Exp. Biol.* 48, 865–878.

Gomes, A., Ghosh, S., Sengupta, J., Saha, K., and Gomes, A. (2018). Nanotechnology in snake venom research-an overview. *Indian J. Exp. Biol.* 56, 707–715.

Gomes, A., Saha, A., Chatterjee, I., and Chakravarty, A. K. (2007). Viper and Cobra venom neutralization by beta-sitosterol and stigmasterol isolated from the root extract of *Puchea indica* Less. *Asteraceae. Phytomedicine* 14 (9), 637–643. doi:10.1016/j.phymed.2006.12.020

Gopi, K., Renu, K., Sannanaik Vishwanath, B., and Jayaraman, G. (2015). Protective effect of Euphorbia hirta and its components against snake venom induced lethality. *J. Ethnopharmacol.* 165, 180–190. doi:10.1016/j.jep.2015.02.044

Guerranti, R., Aguiyi, J. C., Ogueli, I. G., Onorati, G., Neri, S., Rosati, F., et al. (2004). Protection of *Mucuna pruriens* seeds against *Echis carinatus* venom is exerted through a multiform glycoprotein whose oligosaccharide chains are functional in this role. *Biochem. Biophysical Res. Commun.* 323 (2), 484–490. doi:10.1016/j.bbrc.2004.08.122

Gutiérrez, J. M., Albulescu, L.-O., Clare, R. H., Casewell, N. R., Abd El-Aziz, T. M., Escalante, T., et al. (2021). The search for natural and synthetic inhibitors that would complement antivenoms as therapeutics for snakebite envenoming. *Toxins* 13 (7), 451. doi:10.3390/toxins13070451

Gutierrez, J. M., Rucavado, A., Chaves, F., Díaz, C., and Escalante, T. (2009). Experimental pathology of local tissue damage induced by *Bothrops asper* snake venom. *Toxicon* 54 (7), 958–975. doi:10.1016/j.toxicon.2009.01.038

Houghton, P. J., Osibogun, I. M., and Bansal, S. (1992). A peptide from *Schumanniophyton magnificum* with anti-cobra venom activity. *Planta Medica* 58 (3), 263–265. doi:10.1055/s-2006-961449

Houghton, P. J., and Skari, K. P. (1994). The effect on blood clotting of some west African plants used against snakebite. *J. Ethnopharmacol.* 44 (2), 99–108. doi:10.1016/0378-8741(94)90075-2

Huang, Y. K., Chen, Y. C., Liu, C. C., Cheng, H. C., Tu, A. T., and Chang, K. C. (2022). Cerebral complications of snakebite envenoming: case studies. *Toxins* 27 (7), 436. doi:10.3390/toxins14070436

Hung, Y. C., Sava, V., Hong, M. Y., and Huang, G. S. (2004). Inhibitory effects on Phospholipase A2 and antivenin activity of melanin extracted from *Thea sinesis* Linn. *Life Sci.* 74 (16), 2037–2047. doi:10.1016/j.lfs.2003.09.048

Hussain, S. S., and Kingsley, D. (2024). Ethnomedicinal breakthroughs in snake bite therapy: from folklore to forefront. *Toxicol. Rep.* 13, 101795. doi:10.1016/j.toxrep.2024.101795

Izidoro, L. F., Rodrigues, V. M., Rodrigues, R. S., Ferro, R. V., Hamaguchi, A., Giglio, J. R., et al. (2003). Neutralization of some hematological and hemostatic alterations induced by neuwiedase, a metalloproteinase isolated from *Bothrops neuwiedi* pauloensis snake venom by the extract from *Casearia mariquitensis* (Flacourtiaceae). *Biochimie* 85 (7), 669–675. doi:10.1016/s0300-9084(03)00126-3

Januario, A. H., Santos, S. L., Marcussi, S., Mazz, M. V., Pietro, R. C., Sato, D. N., et al. (2004). Neo-clerodane diterpenoid, a new mettaloprotease snake venom inhibitor from *Baccharis trimera* (Asteraceae): anti-proteolytic and anti-hemorrhagic properties. *Chemico-Biological Interact.* 150 (3), 243–251. doi:10.1016/j.cbi.2004.09.016

Jayawardana, S., Arambepola, C., Chang, T., and Gnanathasan, A. (2018). Long-term health complications following snake envenoming. *J. Multidiscip. Healthc.* 11, 279–285. doi:10.2147/JMDH.S126648

Kankara, I. A., Abdullahi, I., and Paulina, G. A. (2020). Ethnomedicinal plants: a source of phytochemical compounds against snake venom PLA2s activity. *J. Pharmacogn. Phytochemistry* 9 (2), 1270–1275.

Kini, R. M., and Gowda, T. (1982). Studies on snake venoms Enzymes: Part 1. Purification of ATPase, a toxic component of *Naja naja* venom, and its inhibition by Potassium gymnemate. *Indian J. Biochem. Biophysics* 19 (2), 152–154.

Knowles, R. (1921). The mechanism and treatment of Snakebite in India. *Transaction R. Soc. Trop. Med. Hygine* 15 (3), 71–97. doi:10.1016/s0035-9203(21)90313-4

Krishnan, S. A., Kumar, R. D., Sankar, A., Nair, S., and Oommend, O. V. (2014). Studies on neutralizing effect of *Ophiorrhiza mungos* root extract against *Daboia russelii* venom. *J. Ethnopharmacol.* 151, 543–547. doi:10.1016/j.jep.2013.11.010

Leanpolchareanchai, J., Pithayanukul, P., Bavovada, R., and Saparpakorn, P. (2009). Molecular docking studies and anti-enzymatic activities of Thai mango seed kernel extract against snake venoms. *Molecules* 14 (4), 1404–1422. doi:10.3390/molecules14041404

Liaqat, T. H., Mallhi, Y. H., Khan, A., Khokhar, S., and Chaman, M. A. (2022). Anti-snake venom property of medicinal plants: a comprehensive review of literature. *Braz. J. Pharm. Sci.* 58. doi:10.1590/s2175-97902022e191124

Machiah, D. K., Girish, K. S., and Gowda, T. V. (2006). A glycoprotein from a folk medicinal plant, *Withania somnifera* inhibits hyaluronidase activity of snake venoms. Comparative Biochemistry Physiology, Part-C. *Toxicol. Pharmacol.* 143 (2), 158–161. doi:10.1016/j.cbpc.2006.01.006

Mahadeswaraswamy, Y. H., Nagaraju, S., Girish, K. S., and Kemparaju, K. (2008). Local tissue destruction and procoagulation properties of *Echis carinatus*: inhibition by *Vitis vinifera* seed methanol extract. *Phytotherapy Res.* 22 (7), 963–269. doi:10.1002/ptr.2462

Mahanta, M., and Mukherjee, A. K. (2001). Neutralization of lethality, myotoxicity, and toxic enzymes of *Naja kaouthia* venom by *Mimosa pudica* root extracts. *J. Ethnopharmacol.* 75 (1), 55–60. doi:10.1016/s0378-8741(00)00373-1

Maiorano, V. A., Marcussi, S., Daher, M. A. F., Oliveira, C. Z., Couto, L. B., Gomes, O. A., et al. (2005). Antiophodian properties of the aqueous extract of *Mikania glomerata*. *J. Ethnopharmacol.* 102 (3), 364–370. doi:10.1016/j.jep.2005.06.039

Makhija, I. K., and Khamar, D. (2010). Anti-snake venom properties of medicinal plants. *Scholars research library, der pharmacia lettre* 2 (5), 399–411.

Memmi, A., Sansa, G., Rjeibi, I., El Ayeb, M., Srairi-Abid, N., Bellasfer, Z., et al. (2007). Use of medicinal plants against scorpionic and ophidian venoms. *Arch. Inst. Pastuer Tunis* 84 (1-4), 49–55.

Mendes, M. M., Oliviera, C. F., Lopes, D. S., Vale, L. H., Alcantara, T. M., Izidoro, L. F., et al. (2008). Anti-snake venom properties of *Schizolobium parahyba* (Caesalpinoidae) aqueous leaves extract. *Phytotherapy Res.* 22 (7), 859–866. doi:10.1002/ptr.2371

Menon, V. P., and Sudheer, A. R. (2007). Anti-oxidant and anti-inflammatory properties of curcumin. *Adv. Exp. Med. Biol.* 595, 105–125. doi:10.1007/978-0-387-46401-5_3

Mhaskar, K. S., and Caius, J. F. (1931). Indian plant remedies in snake bite. *Indian J. Med. Res.* 19, 28.

Mokua, S. K., Mbaria, J. M., Maitho, T. E., and Moriasi, G. A. (2021). Ethnobotanical documentation, phytochemical screening, and cytotoxicity evaluation of medicinal plants used to manage snakebite envenomation in Mwingi West subcounty, Kenya. *Evidence-Based Complementary Altern. Med.* 2021, 4167296. doi:10.1155/2021/4167296

Mors, W. B., do Nascimexito, M. C., Parente, J. P., da Silva, M. H., Melo, P. A., and Suarez –Kurtz, G. (1989). Neutralization of lethal and myotoxic activities of South American rattlesnake venom by extracts and constituents of the plant *Eclipta prostrata* (Asteraceae). *Toxicon* 27 (9), 1003–1009. doi:10.1016/0041-0101(89)90151-7

Mors, W. B., Nascimento, M. C., Perreira, B. M., and Pereira, N. A. (2000). Plant natural products active against snakebite-the molecular approach. *Phytochemistry* 55 (6), 627–642. doi:10.1016/s0031-9422(00)00229-6

Mostafa, M., Nahar, N., Mosihuzzaman, M., Sokeng, S. D., Fatima, N., Atta-Ur-Rahman., et al. (2006). Phosphodiesterase-I inhibitor quinovic acid glycosides from Bridelia ndellensis. *Nat Prod Res.* 20 (7), 686–92. doi:10.1080/14786410600661658

Mukherjee, A. K., Doley, R., and Saikia, D. (2008). Isolation of a snake venom phospholipase A2 (PLA2) inhibitor (AIPLAI) from leaves of *Azadirachta indica* (Neem): mechanism of PLA2 inhibition by AIPLAI *in vitro* condition. *Toxicon* 51 (8), 1548–1553. doi:10.1016/j.toxicon.2008.03.021

Nakagawa, M., Nakanishi, K., Darko, L. L., and Vick, J. A. (1982). Structures of cabenegrins A-I and A-II, potent anti-snake venoms. *Tetrahedron Lett.* 23, 3855–3858. doi:10.1016/s0040-4039(00)87726-6

Narvencar, K. P., Favas, T. T., and Dias, A. (2022). Predictors of complications in venomous snakebites. *Indian J. Med. Sci.* 74, 86–92. doi:10.25259/ijms_328_2021

Nataraju, A., Raghavendra Gowda, C. D., Rajesh, R., and Vishwanath, B. S. (2007). Group IIA secretory PLA2 inhibition by ursolic acid: a potent anti-inflammatory molecule. *Curr. Top. Med. Chem.* 7 (8), 801–809. doi:10.2174/156802607780487696

Nirmal, N., Praba, G. O., and Velmurugan, D. (2008). Modeling studies on Phospholipase A2 –inhibitor complexes. *Indian J. Biochem. Biophysics* 45 (4), 256–262.

Nunez, V., Castro, V., Murillo, R., Ponce-Soto, L. A., Merfort e, I., and Lomonte, B. (2005). Inhibitory effects of Piper umbellatum and Piper peltatum extracts towards myotoxic phospholipases A2 from Bothrops snake venoms: isolation of 4-nerolidylcatechol as active principle. *Phytochemistry* 66, 1017–1025. doi:10.1016/j.phytochem.2005.03.026

Nunez, V., Otero, R., Barona, J., Saldarriaga, M., Osorio, R. G., Fonnegra, R., et al. (2004). Neutralization of the edema–forming, defibrinating, and coagulat effects of *Bothrops asper* venom by extracts of plants used by healers in Colombia. *Braz. J. Med. Biol. Res.* 37 (7), 969–977. doi:10.1590/s0100-879x2004000700005

Ode, O. J., and Asuzu, U. I. (2006). The anti-snake venom activities of the methanolic extract of the bulb of *Crinum jagus* (Amarylladaceae). *Toxicon* 48 (3), 331–342. doi:10.1016/j.toxicon.2006.06.003

Okonogi, T., Hattori, Z., Ogiso, A., and Mitsui, S. (1979). Detoxification by persimmon tannin of snake venoms and bacterial toxins. *Toxicone* 17 (5), 524–527. doi:10.1016/0041-0101(79)90287-3

Oliviera, C. Z., Maiorano, V. A., Marcussi, S., Santana, C. D., Januario, A. H., Lourenco, M. V., et al. (2005). Anticoagulant and antifibrinogenolytic properties of the aqueous extract from Bauhinia forficata against snake venoms. *J. Ethnopharmacol.* 98 (1-2), 213–216. doi:10.1016/j.jep.2004.12.028

Oliveira, I. C. F., de Paula, M. O., Lastra, H. C. B., Alves, B. B., Moreno, D. A. N., Yoshida, E. H., et al. (2019). PActivity of silver nanoparticles on prokaryotic cells and Bothrops jararacussu snake venom. *Drug Chem Toxicol* 42 (1), 60–64. doi:10.1080/01480545.2018.1478850

Omara, T., Nakiguli, C. K., Naiyl, R. A., Opondo, F. A., Otieno, S. B., Ndiege, M. L., et al. (2021). Medicinal plants used as snake venom antidotes in east african community: review and assessment of scientific evidences. *J. Med. Chem. Sci.* 4 (2), 107–144. doi:10.26655/JMCHEMSCI.2021.2.4

Otero, R., Nunez, V., Barona, J., Fonnegra, R., Jimenez, S. L., Osorio, R. G., et al. (2000). Snakebites and ethnobotany in the northwest region of Colombia; Part 3; Neutralization of hemorrhagic effect of Bothrops *atrox* venom. *J. Ethnopharmacol.* 73 (1-2), 233–241. doi:10.1016/s0378-8741(00)00321-4

Patricia, S. O., José, M., Gutiérrez, Y. O., and Hay, A. C. (2022). Neutralization of toxic activities of *Bothrops asper* venom by plants of ethnomedical use in Central America: plants collected in Guatemala Cienc. *Tecnol. ía Y. Salud* 9 (2), 215–236. doi:10.36829/63cts.v9i2.922

Pithayanukul, P., Laovachirasuwan, S., Bavovada, R., Pakmanee, N., and Suttisri, R. (2004). Antivenom potential of butanolic extract of *Eclipta prostrata* against Malyalan pit viper. *J. Ethnopharmacol.* 90 (2-3), 347–352. doi:10.1016/j.jep.2003.10.014

Pithayanukul, P., Ruenraroengsak, P., Bavovada, R., Pakmanee, N., Suttisri, R., and Saen-oon, S. (2005). Inhibition of *Naja kaouthia* venom activities by plant polyphenols. *J. Ethnopharmacol.* 97 (3), 527–533. doi:10.1016/j.jep.2004.12.013

Preciadoa, L. M., Rey-Suáreza, P., Henaob, I. C., and Pereañeza, J. A. (2018). Betulinic, oleanolic, and ursolic acids inhibit the enzymatic and biological effects induced by a P-I snake venom metalloproteinase. *Chemico-Biological Interact.* 279, 219–226. doi:10.1016/j.cbi.2017.12.001

Raslan, D. S., Jamal, C. M., Duarte, D. S., Borges, M. H., and De Lima, M. E. (2002). Anti-PLA2 action test of Casearia sylvestris Sw. *Boll. Chim. Farm.* 141, 457–460.

Ratanabanangkoon, K., Cherdchu, C., and Chudapongse, P. (1993). Studies on the cobra neurotoxin inhibiting activity in an extract of Curcuma sp. (Zingiberaceae) rhizome. *Southeast Asian J. Trop. Med. Public Health* 24 (1), 178–185.

Reis, F. P., Senna Bonfa, I. M., Cavalcante, R. B., Okoba, D., de Souza Vasconcelos, S. B., Candeloro, L., et al. (2014). Tabebuia aurea decreases inflammatory, myotoxic and hemorrhagic activities induced by the venom of Bothrops neuwiedi. *J. Ethnopharmacol.* 158, 352–357. doi:10.1016/j.jep.2014.10.045

Reyes –Chilpa, R., Gomez –Garibay, F., Quijano, L., Magos-Guerrero, G. A., and Rios, T. (1992). Preliminary results on the protective effects of edunol, a pterocarpan from *Brongniartia podalyrioides* (Leguminosae), against *Bothrops atrox* venom in mice. *J. Ethnopharmacol.* 42, 199–203. doi:10.1016/0378-8741(94)90086-8

Rhamy, T. R., and Hemmaid, K. Z. (2001). Prophylactic action of garlic on the histological and histochemical patterns of hepatic and gastric tissues in rats injected with a snake venom. *J. Nat. Toxins* 10 (2), 137–165.

Rivel, M., Solano, D., Herrera, M., Vargas, M., Villalta, M., Segura, A., et al. (2016). Pathogenesis of dermonecrosis induced by venom of the spitting cobra, *Naja nigricollis*: an experimental study in mice. *Toxicon* 119, 171–179. doi:10.1016/j.toxicon.2016.06.006

Rucavado, A., Soto, M., Escalante, T., Loría, G. D., Arni, R., and Gutiérrez, J. M. (2005). Thrombocytopenia and platelet hypoaggregation induced by *Bothrops asper* snake venom. Toxins involved and their contribution to metalloproteinase-induced pulmonary hemorrhage. *Thromb. Haemost.* 94 (1), 123–131. doi:10.1160/TH05-02-0112

Saha, K., Ghosh, S., Ghosh, S., Dasgupta, S. C., Gomes, A., and Gomes, A. (2015). Neutralization of *Naja Kaouthia* venom-induced acute toxicity and stress response with herbal gold nanoparticle (VN-GNP) in experimental animal models. *J. Toxins* 2 (1), 8.

Saha, K., and Gomes, A. (2017). Russel' 's viper venom-induced nephrotoxicity, myotoxicity, hepatotoxicity: neutralization with gold nanoparticle conjugated 2-hydroxy-4-methoxy benzoic acid (GNP-HMBA) in the experimental animal model. *Indian J. Exp. Biol.* 55 (1), 7–14.

Samy, R. P., Thwin, M. M., Gopalakrishnakone, P., and Ignacimuthu, S. (2008). Ethnobotanical survey of folk plants for the treatment of snakebites in Southern part of Tamilnadu, India. *J. Ethnopharmacol.* 115 (2), 302–312. doi:10.1016/j.jep.2007.10.006

Sani, I., Bello, F., Fakai, I. M., and Abdulhamid, A. (2020). Evaluation of antisnake venom activities of some medicinal plants using albino rats. *J. Traditional Complementary Med.* 3 (6), 111–117. doi:10.36348/sijtcm.2020.v03i06.001

Selvanayagam, Z. E., Gnanavendhan, S. G., Balakrishna, K., Rao, R. B., Sivaraman, J., Subramanian, K., et al. (1996). Ehretianone, a novel quinonoid xanthene from *Ehretia buxifolia* with antisnake venom activity. *J. Nat. Prod.* 59 (7), 664–667. doi:10.1021/np960355p

Senji Laxme, R. R., Khochare, S., de Souza, H. F., Ahuja, B., Suranse, V., Martin, G., et al. (2019). Beyond the "big four": venom profiling of the medically important yet neglected Indian snakes reveals disturbing antivenom deficiencies. *PLoS Neglected Trop. Dis.* 13 (12), e0007899. doi:10.1371/journal.pntd.0007899

Shirwaikar, A., Rajendran, K., Bodla, R., and Kumar, C. D. (2004). Neutralization potential of *Viper russeli (Russels viper)* venom by ethanol leaf extract of *Acalypha indica L. J. Ethnopharmacol.* 94 (2-3), 267–273. doi:10.1016/j.jep.2004.05.010

Shivashankar, S., Murali, A., and Sangeetha, M. K. (2019). Molecular interaction of phytochemicals with snake venom: Phytochemicals of Andrographis paniculata inhibits phospholipase A2 of Russell's viper (Daboia russelli). *Biocatalysis and Agricultural Biotechnology* 18, 101058. doi:10.1016/j.bcab.2019.101058

Shukla, A. N., Srivastava, S., and Rawat, A. K. S. (2010). An ethnobotanical study of medicinal plants of Rewa district, Madhya Pradesh. *Indian J. Traditional Knowl.* 9 (1), 191–202.

Simpson, I. A. (2008). A study of the current knowledge base in treating snakebites amongst doctors in the high-risk countries of India and Pakistan: does snake bite treatment training reflect local requirements? *Trans. R. Soc. Trop. Med. Hyg.* 102, 1108–1114. doi:10.1016/j.trstmh.2008.04.013

Soares, A. M., Fontes, R. M., and Giglio, J. R. (2004). Phospholipase A2 myotoxins from Bothrops snake venoms: structure- function relationship. *Curr. Org. Chem.* 8, 1677–1690. doi:10.2174/1385272043369610

Soares, K. S. R., Glaucia-Silva, F., Daniele-Silva, A., Torres-Rego, M., Araujo, N. K., Menezes, Y. A. S., et al. (2018). Antivenom production against *Bothrops jararaca* and *Bothrops erythromelas* snake venoms using cross-linked chitosan nanoparticles as an immunoadjuvant. *Toxins (Basel)* 10 (4), 158. doi:10.3390/toxins10040158

Soni, P., and Bodakhe, S. H. (2014). Antivenom potential of ethanolic extract of Cordia macleodii bark against Naja venom. *Asian Pac J. Trop. Biomed.* 4 (Suppl. 1), S449–S454. doi:10.12980/APJTB.4.2014C1048

Sulabh, S., and Shivahre, P. R. (2018). Common poisonous snakes of India - a review. *World J. Pharm. Res.* 7, 431–442.

Suraweera, W., Warrell, D., Whitaker, R., Menon, G., Rodrigues, R., Fu, S. H., et al. (2020). Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study. *Elife* 9, e54076. doi:10.7554/eLife.54076

Ticli, F. K., Hage, L. I., Cambraia, R. S., Pereira, P. S., Magro, A. J., Fontes, M. R., et al. (2005). Rosmarinic acid, a new snake venom phospholipase A2 inhibitor from *Cordia verbenaceae* (Boraginaceae): antiserum action potentiation and molecular interaction. *Toxicon* 46 (3), 318–327. doi:10.1016/j.toxicon.2005.04.023

Uetz, P., Freed, P., and Hošek, J. (2020). The reptile database. Available at: http://www.reptile-database.org (Accessed September 24, 2020).

Ushanandini, S., Nagaraju, S., Harish, K. K., Vedavathi, M., Machiah, D. K., Kemparaju, K., et al. (2006). The anti-snake venom properties of *Tamarindus indica* (Leguminosae) seed extract. *Phytotherapy Res.* 20 (10), 851–858. doi:10.1002/ptr.1951

Usubillaga, N., Khouri, S., and Yibirin, E. (2005). Anti snake venom effect of *Aristolochia odoratissima* L. aqueous extract on mice. *Acta Hortic.* 85 (3), 677. doi:10.17660/actahortic.2005.677.11

Vale, L. H., Mendes, M. M., Hamaguchi, A., Soares, A. M., Rodrigues, V. M., and eburgo, M. I. (2008). Neutralization of pharmacological and toxic activities of *Bothrops* snake venoms by *Schizolobium parahyba* (Fabaceae) aqueous extract and its fractions. *Basic Clin. Pharmacol. Toxicol.* 103 (1), 104–107. doi:10.1111/j.1742-7843.2008.00248.x

Veronese, E. L., Esmeraldino, L. E., Trombone, A. P., Santana, A. E., Bechara, G. H., Ketulhut, I., et al. (2005). Inhibition of the myotoxic activity of *Bothrops jararacussu* venom and its two major myotoxins BthTX 1 and BthTX2, by the aqueous extract of *Taberenaemontana catherinensis* A. D.C., (Apocynaceae). *Phytomedicine* 12 (1-2), 123–130. doi:10.1016/j.phymed.2003.07.010

Vishwanath, B. S., Rao, A. G., and Gowda, T. V. (1987). Interaction of phospholipase A from Vipera russelli with aristolochic acid: a circular dicroism study. *Toxicon* 25, 939–946. doi:10.1016/0041-0101(87)90156-5

Wagner, H., Geyer, B., Kiso, Y., Hikino, H., and Rao, G. S. (1986). Coumestans as the main active principles of the liver drugs *Eclipta alba* and *Wedelia calendulaceae* 1. *Planta Medica* 52 (5), 370–374. doi:10.1055/s-2007-969188

World Health Organization (2021). Snakebite envenoming: prevalence of snakebite envenoming. 2021. Available at: https://www.who.int/snakebites/epidemiology/.

Xiong, Y., Li, B., Huang, D., He, Q., and Yu, X. C. (2018). Anti- Deinagkistrodon acutus venom properties of ethanolic root extract from Cynanchum paniculatum (Bunge) kitag and its GC-MS analysis. *J. Ethnopharmacol.* 225, 189–197. doi:10.1016/j.jep.2018.07.002

Yang, L. C., Wang, F., and Liu, M. (1998). A study of an endothelin antagonist from a Chinese anti-snake venom medicinal herb. *J. Cardiovasc. Pharmacol.* 31 (Suppl. 1), 249–250. doi:10.1097/00005344-199800001-00070

Yeagle, P. L. (1985). Cholesterol and the cell membrane. *Biochimica Biophysica Acta (BBA) - Rev. Biomembr.* 822 (Issues 3–4), 267–287. doi:10.1016/0304-4157(85)90011-5