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Review Article

Herbal Antivenins as an Eye Opener towards Snake Envenomation

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Abstract

Snakebites are the most neglected health problem in India. Antivenoms are used in treatment, but since they are mostly unavailable, the mortality rate is even higher in rural areas. The currently available antivenoms are monovalent and polyvalent and are effective against four common snakes in India. In this article, we have reviewed the herbal antivenoms against specific snake species along with their in vitro and in vivo studies and the phytochemicals responsible for antivenom activity. These phytochemicals have been scientifically proven to neutralize the effects of deadly snake venoms and can be used as an adjunct to anti snake venom therapy or can be effectively used to provide proper first aid in snake bite cases to decrease the mortality rates. Studies have been conducted on plant extracts to explore their antivenom activity along with anti myotoxic, anti haemorraghic as well as anti inflammatory activity. These herbs are used ethnopharmacologically by traditional healers for snake envenomations. The review here is a comprehensive approach to the phytochemicals having anti venom activity, however, further studies are needed to gain in-depth knowledge.

Keywords: *Antivenoms, Ethnopharmacology, Herbal antidotes, Snakebites.*

Introduction

The life-threatening condition that occurs whenever snakebites occur has troubled humanity since its inception. According to a recent global report, approximately 5.5 million snakebites are recorded each year, resulting in 2 million deaths (Bulfone *et al.,* 2018). Farmers and kids being more vulnerable, but the kids suffer to greater due to smaller body mass. The gender profile of snake bite patients showed that adult males are in the highest risk group 64% while young women and female children are low risk group around 3.5% (Whitaker, 2006).

Snakes are carnivorous reptiles of the suborder Serpents; these have a skull with multiple joints, which enables them to devour their prey. Although 3700 species of snakes are found on Earth, only 15percent are dangerous to humans, i.e., most of them are non- venomous, and some have venom sufficient to kill prey or are potent enough to cause death in humans. In this context, antivenin therapy is gaining importance, especially for the herbal medicines that are unexplored in the modern world (Sani, Fakai & Abdulhamid, 2020).

Snake venom is a lethal mixture of neurotoxins, hemotoxins, cytotoxins, and bugarotoxins. They also contain the enzyme hyaluronidase, which causes rapid diffusion of the venom. The venom is secreted in their parotid salivary glands and delivered through hollow fangs that act like needles and are forced out of the glands by the head muscles (Omara *et al.,* 2020).

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Venomous snakes

The venomous snakes are divided into elapids - cobras, Viperids - vipers, Colubirds – boomslangs. List of common poisonous snakes given in table 1. (Sulochana *et al.,* 2015).

Table 1. List of common poisonous snakes in India

Common name	Scientific name
Indian cobra	*Naja naja*
Common krait	*Bungarus caeruleus*
Russells viper	*Daboia russelii*
Saw-scaled viper	*Echis carinatus*
Indian banded krait	*Bungarus fasciatus*

When bitten by a venomous snake, there is a severe burning pain that develops into local tissue damage at the bite site, followed by respiratory distress, weak pulse, visual disturbances, CVS, renal changes, etc.

Antivenom Therapy

Antivenom therapy is the specific treatment that can potentially reverse the effects of a snake bite when administered at an appropriate therapeutic dose according to the WHO. These are purified antibodies against venom or venom components. In addition, artificial respiration, dialysis, re constitutive surgery, and prosthetics can be given. However, first and foremost, the conformation of the snake species that bit should be diagnosed (Upasani *et al.,* 2018).

Australia is one of the first and leading countries in the world to experiment with snake venom, and the country has developed snake venom detection kits to help select the appropriate antivenom required (Bhattacherjee *et al.,* 2011).

Antivenom is a suspension of antibodies prepared from hyper-immunized horses against a single species of snake venom - monovalent ASV or the venom of several species - polyvalent ASV. However, it can cause adverse drug reactions within 24 hours of administration or later. The ASV suspension has a half-life of 2 years and must be stored at 0-4 °C to prevent deterioration. These antivenoms are not readily available in areas where they are most needed (Goutham *et al.,* 2014).

Side effects include anaphylactic reactions, skin flushing, facial swelling, difficulty breathing, joint inflammation, lymph gland enlargement, fever, unusual fatigue, and weakness (Adriao *et al.,* 2022).

Cocktail concept

Extracts from 5 different plants, such as *A. catechu, C. serratum, A. indica, B. monosperma,* and *C. limonis,* with pronounced anti-edematous, antihemorrhagic, and antimyotoxic effects, were combined to act synergistically against the four major snakes of India, namely krait, cobra, saw-scaled viper, and russell viper. The concept was to choose a polyherbal formulation, which has been shown to be more effective than a formulation containing a single herbal extract. However, herbal extracts that can be used as antidotes to the particular snake venom are still more important (Vasudev *et al.,* 2021).

In this scenario, there is a need for a new approach such as cocktail therapy or small molecule therapeutics with minimal adverse reactions. In this review, some aspects of antivenom therapy from medicinal plants are listed. There are several scientifically based studies demonstrating plants as potential agents with promising antivenom activity.

A project established by WHO in the year 2017 with the strategy that aims at developing road map on snake bites. This focused on reducing the mortality and disability caused by snake bite envenoming up to 80% by the year 2030.

Herbs as a first aid in managing snake bite

According to ethnical knowledge plants like *Acorus calamus, Achyranthes aspera, Bombax ceiba, Buchanania lanzan, Gynandropsis gynandra, Moringa oleifera* can be made into a paste and applied locally on snake bit area of the affected person since they can act as an effective antidote.

Method

Broad level of literature search was performed with prime focus on peer reviewed journal articles also analysis and sorting was done systematically keeping in mind the 5 C's rule of conducting review.

Discussion

Adriao *et al*. (2022) investigated plant-derived toxin inhibitors as potential candidates to supplement antivenom treatment in snake bite envenomation's. Maria *et al.(*2021) validated the antivenom action of *Alstonia parviflolia*. Bhat et al. investigated the antivenom activity of *Cassia alata* leaf extract against the venom of *Daboia russellii*. Sani *et* al.(2020) studied the lethality of Naja nigricolis venom and investigated the antivenom activity of *Azadirachta indica* on albino rats. Veena More *et al*., evaluated the antivenom potential of *Areca catechu* seed extract against *Bungarus caeruleus* venom. The antivenom activity of *Moringa oleifera* leaves against pathophysiological alterations, somatic mutations, and biological changes of *Naja nigricolis* venom was studied by Adeyi *et al*.2000 (Table 2).

Clerodendron infortunatum

The ethanolic extract of the leaves of *Clerodendron infortunatum* (figure 1) shows the presence of flavonoids which are known for their antioxidant activity hence DPPH radical scavenging activity, FRAP assay and Hydrogen peroxide radical scavenging activity was studied. Accordingly promising results were obtained which further needs to be developed towards isolation and characterization of active bio molecule responsible for the activity (Modi *et al.,* 2010). This antioxidant activity in turn contributes to anti venom nature (Wang *et al.,* 2018).

Ophiorrhiza mungos

The plant (figure 2) especially the root extract, has long been used in traditional folk medicine for its antivenom effects. This snake venom neutralizing effect and traditional form were studied in chick embryos. The disc impregnated with snake venom and extract at different concentrations was applied to chick embryos and its membrane stabilizing property was studied by HRBC lysis method. After 6 days of incubation, 100% recovery was observed; moreover, the extract was found to eliminate even traces of hemorrhagic lesions induced by the venom at high concentrations (Krishnan *et al.,* 2014).

Andrographis paniculata

This extract proved of the plant (figure 3) to be effective against the venom of Daboia russelli, especially due to its pharmacological properties that can counteract effects such as edema, hemorrhagic, coagulant, fibrinolytic and phospholipase activities. The methanolic extract used for in vivo evaluation was injected into the tail vein of mice, 3-5 mice per group at different doses. The median lethal dose was calculated based on the number of deaths within 24hours of injection (Meenatchisundaram *et al.,* 2009). The extract was found to be effective in neutralizing the Russel's viper- induced defibrinogenating activity. A significant decrease in foot paw edema was also noted when the concentration of the extract was increased (Salwe *et al.,* 2011).

Mucuna pruriens

The antivenom potential of *Mucuna pruriens* (figure 4) was studied against cobra snake venom. The plant was found to contain various phytochemicals such as saponins, flavonoids, steroids, alkaloids and anthraquinones. There was a much reduction in cholesterol, AST, ALT, bilirubin, catalase as well as glutathione in envenomed mice after 14days of treatment. A dose of 80mg/kg proved more effective than the standard drug, suggesting that the extract has greater antivenom potential than commercial antivenom (Shekins *et al.,* 2014).

Azima tetracantha

Ethyl acetate extract of *Azima tetracantha* (figure 5) leaves contains compounds that inhibit the activity of toxic enzymes of Bungarus caeruleus and Vipera russelli. Vacuum-dried extract was used for the study. Preliminary phytochemical screening revealed the presence of flavonoids, phytosterols, and proteins. Ezymatic inhibition studies showed that the extract was able to inhibit the enzymes phospodiesterase, phosphomonoesterase, acetylcholinesterase, nucleotides, phospholipase A_2, and hyaluronidase in the venom at a concentration of 100µg/ml (Janardhan *et al.,* 2014).

Calotrophis gigantea

The plant *Calotrophis gignatea* (figure 6) used against edema induced by viperoid venom was studied. The extract at various doses when orally given to rats inhibited the haemorrhagic and necrotic effect by the venom. Significant antinecrotic activity was noted at doses ranging from 200 to 400mg/kg. In vitro studies also neutralized the effect of the venom. It showed a significant anti-inflammatory effect comparable to that of antivenom (Chacko *et al.*, 2012).

Moringa oleifera

Moringa oleifera (figure 7) contains flavonoids, alkaloids, terpenoids, saponins and tannins. Treatment with the antivenom results in a significant decrease in the number of leukocytes, neutrophils and monocytes compared to the untreated groups. It also showed a lowered plasma levels of AST, ALT and GGT. It decreased bleeding time but there was no inhibition of hemolysis. It also prolonged the clotting time, indicating the blood-promoting effect. The hematopoietic properties is because of the vitamins B2, C (Adaji *et al.*, 2020).

Piper longum

The plant (figure 8) is traditionally used in India for snakebites (Yadav *et al.,* 2020). Mouse sera were tested for antibodies to Russell's viper venom using in vitro and in vivo neutralisation tests. Mice treated with piperine were found to inhibit the lethal effect of venom bites. Immunization with the ethanolic extract of the fruits of Piper longum and piperine resulted in a high antibody titer against the venom. The presence of antibodies to the venom was confirmed by ELISA and double immuno diffusion assays (Shenoy *et al.,* 2013).

Alstonia parvifolia

The bark extract of the plant (figure 9) shows its cytotoxicity by PLA_2 inhibition, DPPH and cytotoxicity assays. Using GC-MS analysis, the constituents were determined. Molecular docking studies were performed to determine the binding energies between the selected compounds and PLA_2 isoforms, and affinity was determined based on dipole interactions with amino acid residues. Six bioactive compounds were present in the crude extract. The alkaloids, particularly the indole alkaloids in the extract showed their suppressive effects on the PLA_2 enzyme and the hyaluronidase enzyme. The extract also contained phytosterols, which are responsible for the myotoxic activities (Maria *et al.,* 2021).

Anacardium humile

The isolation of gallic acid from *Anacardium humile* (figure 10) which is a myotoxin inhibitor was done from *Anacardium humile* done by analytical chromatographic method and was confirmed in NMR spectral studies.The compound was found to inhibit myotoxicity induces by Bothrops jararacussu venom. Circular dichorism, fluorescence spectroscopy, dynamic light scattering and molecular docking studies revealed that gallic acid forms a complex with the myotoxins present in the venom (Costa *et al.,* 2021).

Alstonia venenata

The ethanolic extract of the plant (figure 11) was rich in alkaloids, flavonoids, tannins, proteins, carbohydrates, triterpenoids, proteins, amino acids and sterols. The extract was tested for its antivenom action against naja naja venom induced toxic reaction by in-vitro and in-vivo methods. The 200 and 400mg/kg of the extract neutralized the lethality induced by the venom. Fibrinolytic activity was also performed to determine the activity of the extract when the blood was treated with venom (Venkatesh & Sreelakshmi, 2019).

Cordia macleodii

The ethanolic extract of *Cordia macleodii* (figure 12) extract was effective in neutralizing the coagulant and defibrinogenating activity of snake venom. The cardiotoxic experiments on isolated frog heart as well as the neurotoxic effects frog rectus abdominus muscle experiments were antagonized by the plant extract. The haemorraghic lesion, necrotising lesion and edema in rats was inhibited at a particular dose of the extract. Hereby it was evident that the extract of Cordia macleodii against naja naja venom by the cardiotonic, proteolysin neutralization, anti inflammatory, anti serotonic and anti histaminic activity. These effects are due to precipitation of venom constituents (Soni & Bodakhe, 2014).

Areca catechu

The seed extract of the plant (figure 13) are used to treat various aliments traditionally. The ethyl acetate and aqueous extract of the*A. catechu* seeds was tested for its activity against krait venom. The extract was found to inhibit enzymes like hyaluronidase, protease and phospholipase A_2. In addition the extract also showed promising effects against hemolytic and bleeding action caused by the venom. The extract increased the survival of mice, also neutralized the myotoxic activity. The study was performed on 6 day old chicken embryo and it was found out that the seed extract was not toxic. Thus the survivability of the eggs was extended which was evident when pre incubated with krait venom and seed extract in different ratios (More *et al.,* 2022).

Tamarindus indica

The plant (figure 14) well known traditionally was chosen to test its efficacy against snake venom. Initially the seed coat extract confirmed the presence of secondary metabolites. The inhibitory action of the following enzymes like phospholipase A_2, haemorraghic, procoagulant, proteolytic were performed. Snake venom contains many neurotoxic, myotoxic, haemorraghic and coagulant compounds that reacts systematically on the victim resulting in death. Upon administration of the extract the mice showed complete survival of mice due to total venom neutralizing effect. The extract maybe used in topical pharmaceutical formulation that will reduce local venom reactions causing much morbidity which will along with the antivenom causes envenomation to be more effective (Munde *et al.,* 2021).

Justicia adhatoda

The acetone extract of *J. adhatoda* (figure 15) leaves was found to inhibit venom enzyms like 5' nucleotidase, phosphomonoesterase, phosphodiesterase, acetylcholine esterase and hyaluronidase due to the Russels viper venom in a dose dependent manner. The concentration of 250mg of extract showed maximum inhibition of all the enzymes under scrutiny. The 5' nucleotidase is involved in homeostatic alterations by inducing anti coagulant effect by interacting with intrinsic factors of haemostasis (Malathi *et al.,* 2019).

Figure 1. *Clerodendron infortunatum*

Figure 2.*Ophiorrhiza mungos*

Figure 3. *Andrographis paniculata*

Figure 4.*Mucuna pruriens*

Figure 5. *Azima tetracantha*

Figure 6. *Calotrophis gignatea*

Figure 7. *Moringa oleifera*

Figure 8. *Piper longum*

Figure 9. *Alstonia parvifolia*

Figure 10. *Anacardium humile*

Figure 11.*Alstonia venenata*

Figure 12. *Cordia macleodii*

Figure 13.*Areca catechu*

Figure 14. *Tamarindus indicus*

Figure 15. *Justicia adhatoda*

Table 2. Traditional herbs with antivenom activity

Vernacular name	Scientific name	Family	Secondary metaboite responsible for antivenom activity	Reference
Mongoose plant	*Ophiorrhiza mungos*	Rubiaceae	Alkaloids	Krishnan et al., 2014
Drumstick tree	*Moringa oleifera*	Moringaceae	Alkaloids, Saponins	Adeyi et al.,2020
Indian long pepper	*Piper longum*	Piperaceae	Alkaloids	Yadav et al., 2020
Velvet bean	*Mucuna pruriens*	Fabaceae	Alkaloids	Shekins et al., 2014
Prickly chaff flower	*Achyranthes aspera*	Amaranthaceae	Glycosides, Alkaloids and Saponins	Barma et al., 2014
Indian pulai	*Alstonia parvifolia*	Apocyanaceae	Phytosterols and Alkaloids	Maria et al., 2021
Bael	*Aegle marmelos*	Rutaceae	Alkaloids	Barma et al., 2014
Mountain knot grass	*Aerva lanata*	Amaranthaceae	Alkaloids and Flavonoids	Adriao et al., 2022
Bugloss chiretta	*Andrographis echioides*	Acanthaceae	Carbohydrates and Alkaloids	Meenatchisundaram et al., 2009
Crown flower	*Calotrophis gigantea*	Apocyanaceae	Glycosides, Cardenolides and Terpenes	Chacko et al., 2012
Bee sting bush	*Azima tetracantha*	Salvadoraceae	Phytosterols	Janardhan et al., 2014

The numbers of snake bite in India is explained in figure 16. Around 1.2 million snake bite cases have been reported within the last 20years out of which 602,000 males and 565,000 are females.

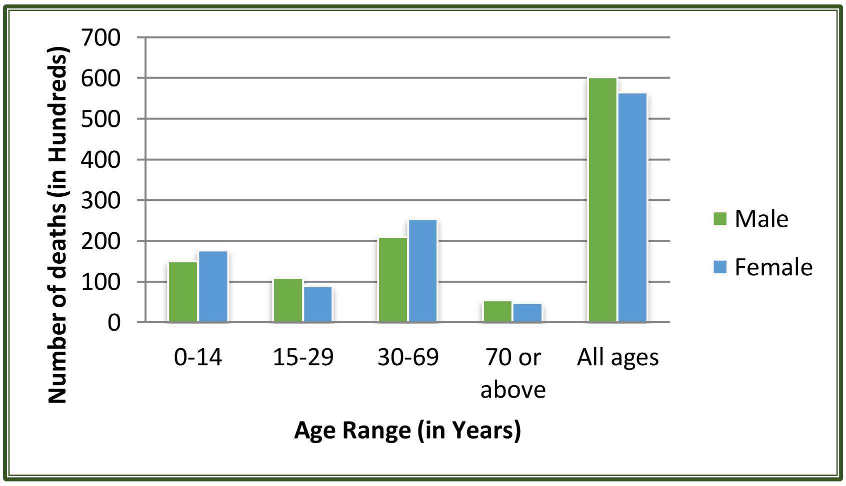

Figure 16. Age wise data of snake bite cases in India
(*Source : Author drawn based on data available from Suraweera et al. 2020.*)

Under reporting of the snake bite incidence leads to difficulty in accurately determining the need for antivenom by the officially authorized health care people which in turn caused a lesser demand hence the antivenom production also affected accordingly. Hence many production units were forced to shut down. All of these led to increased cost of antivenom products due to lesser companies involved in the making of such preparations (Barma *et al.*, 2014).

Conclusion

Lesser price, more accessability, zero issues regarding stability and wide range anti venom activity makes herbs a favourable choice for snake envenomation. These herbal antidotes can be used as first aid remedies for snakebites, preventing the lethal effects of cardiac, neuronal, nephrotic, hemorrhagic, myotoxic, and respiratory effects caused by snake venom. Various plant parts such as roots, rhizomes, bark, fruits, leaves, etc. are used to produce the effect. Several constituents of plants, especially alkaloids, glycosides and flavonoids, are responsible for antivenom activity.In summary, polyvalent antivenom serum to neutralize the venom effect throughout the body where is spreads through the circulatory system and herbal medicament at the site of snake bite to combat necrotic effect will be more accurate. This combination of herbal compounds with antivenom serum will be the only effective way in neutralizing snake venom

Limitations

These plants with antivenom properties are effective agents but have some limitations due to their lethal effects on experimental animals. In all the cases of antivenom activity studies with herbal extracts one thing to be noted is that the herbal extract is to be delivered to the experimental animal prior to venom administration which seems exact opposite when compared to the other in-vivo studies.

Future Research Scope

Further emphasis is needed on identification and isolation of bio molecules will contribute to better understanding of their antivenom activity which remains incomplete in many cases. Till date proper herbal medicament for snake envenomation is not validated and further research work needs to be done.

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Conflict of Interests

Authors declares no conflict of interests.

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