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REVIEW ARTICLE

Antivenomous Plants to Treat The Snakebite Envenomation: An Updated Review

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ABSTRACT
Best treatment of snakebite envenomation is not always available especially in remote and rural areas throughout the world this is often posing a challenge to health care systems. It affects different asian-african developing countries and cultures. These countries still rely on Traditional and folklore knowledge, especially in treatment of snakebite, where healers or specialists on ethnobotany propose plants for the treatment. Although these medicines are traditionally employed as plants against snakebites, this is not well established in many developed countries, because of heavy competition between powerful pharmaceutical companies who are specialists in producing antivenoms. Still number of plants with anti-venom properties has been investigated, with a huge number yet to be explored for such use. The aim of this study is to review relevant publications on anti-venom plants, some with known active molecules already isolated and explored, yet with no intention of exhausting the subject thus in this present article an endeavour has been made to explain the medicinal plants that are either used as tribal/traditional medicines or has already been proved to be useful in the treatment of venomous snakebites with a special emphasis on the isolated phytocompounds responsible for anti-venom activity.

Key-words:- *Folklore Medicines, Snakebites, Phytochemicals, Anti-venoms*

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INTRODUCTION

Venomous snakebites represent a significant health problem, especially in tropical countries, where they frequently affect young and economically active men working in the countryside. [1] Snake bite is a major public health problem in many countries though; it is difficult to talk about the exact number of cases. It is often estimated that the true incidence of snake envenomation cases could exceed few million per year and many of these develop severe complications [2]. The global views in the epidemiological data reflect variations in healthcare reporting as far as accuracy is concerned as well as the diversity of economic and ecological conditions are considered. Accurate records to determine the exact epidemiology or even mortality of snake bite cases are generally unavailable [3]. Hospital records fall far short of the actual number, owing to dependence on traditional healers and practitioners of witchcraft, especially in developing countries. It has been reported that in most developing countries, up to 80% of individuals bitten by snakes first consult traditional practitioners before visiting a medical centre. Owing to the delay, several victims die during journey to the hospital [4].

Envenoming by snakes such as *Vipera russelli* and *Naja naja* are responsible for several clinical complications of severe systemic and local pathology. For example; *Vipera russelli* lead to inflammation (such as swelling, blistering and necrosis) and haemorrhages due to some active enzymes. On the other hand envenoming by *Naja naja* induced clinical complications differ from that caused by *Vipera russelli*. These include neurotoxicity, local necrosis, haemorrhage, complement depletion and respiratory arrest or paralysis. Moreover, the venom of the *Naja naja* consist of phospholipase A2 (an anticoagulant enzymes which inhibit the prothrombinase complex by its binding to coagulation factor Xa). Furthermore,

in some cases envenoming by *Naja naja* can induce corneal ulceration. Although, an intravenous administration of anti-venom, prepared from IgG of venom immunized horses or sheep, is an effective treatment for systemic envenoming, the clinical consensus is that anti-venom is of limited effectiveness against the effects of local envenoming that develop rapidly after a bite. Such effects include severe pain, oedema, localized haemorrhage and necrosis which often results in permanent scarring and deformity. The ineffectiveness of anti-venom in treating local envenoming has been attributed to the rapid activity of the toxins and the inability of anti-venom IgG to cross the blood/tissue barrier. Despite their smaller size Fab fragments of IgG are also ineffective against the local effects of envenoming, whether administered by intravenous or intramuscular routes. Research to develop a treatment for local envenoming is therefore a clinical priority and has focused on the application of natural or synthetic inhibitors of snake venom. The use of plant remedies to treat snakebite victims in rural areas and poor communities in the developing countries is a common practice [5]. The natives who are predominantly rural farmers come in contact with snakes during their farming engagements. Due to high cost of hospital treatment and unavailability of anti-venoms, most often the rural people find it more convenient to consult native doctors who are acclaimed for curing snakebite patients. This evidence indicates that plant remedies used by the native doctors are effective, and there appears to be a high rate of survival among snakebite patients advanced clinical stages of venom toxicity [6].

COMMON POISONOUS SNAKES IN INDIA

Cobra, Krait, Russells viper and Saw Scaled Viper are the four common venomous snake species that are found in India. They are identified as follows,

Fig 1. Common Poisonous Snakes in India (Image Source – Google Images)

1. **Cobra** - Cobras are medium size to large, smooth shiny scales, wide head and neck, wide black band on underside of neck, Distinctive hood mark on top of the neck.

2. **Krait** - Kraits are medium sized with an average length of 1m and smooth, glossy bluish black snakes with the rounded head slightly distinct from the neck. There are normally about 40 thin white cross bands.
3. **Russells viper** - Russells viper are medium sized to large, strongly keeled scales, distinctive bright chain pattern, large triangular head.
4. **Saw scaled viper** - Saw scaled vipers are small, strongly keeled scales, head wider than neck, dull colour, cross mark on top of the head. [23]

ANTISNAKEVENOM AND ITS LIMITATIONS

Currently, the only available treatment for snakebite envenomation is intravenous administration of antisnakevenoms with readymade antibodies or antibody fragments derived from the plasma of mammals (normally, horses) that have been previously immunized with non-lethal venomous doses. These animals produce antibodies against the venom proteins and serum is extracted from their blood for the treatment of envenomation. Conventional serum therapy aims to bind and neutralize the snake venom proteins [24]. It is a fact that the antivenom allows the body to try to reverse the damage caused by the snake venom. However, it is known that such therapy can cause problems related to different antivenom characteristics, such as:

- Limited efficacy of antivenom therapy to protect the affected organ/s against immediate local tissue damage and low stability;
- Ineffectiveness of the antivenom due to significant geographic variation in the composition of the venom;
- Immediate hypersensitivity reaction to the alien immunoglobulins
- Anaphylactic and pyrogenic reactions such as chills, rigor, headache, and tachycardia.
- Delayed antivenom reactions or serum sickness is observed after 8 to 12 days of treatment;
- Cutaneous eruptions, fever, and allergies, among other effects
- Antigenic reactivity due to the taxonomic diversity of the snakes
- Improper use of the antivenom due to incorrect medical management, which contributes to a high incidence of adverse reactions, a low toxin neutralizing potency, or both. [24]

ANTISNAKEVENOM AVAILABILITY AND ISSUES IN STOCKPILING

Manufacture of antidotes from hyperimmunized animals is another problem that affects the access and use of antidotes in rural populations, mainly in developing countries. There is a deficiency in the availability of antidotes and lack of training in the clinical staff, worsening the consequences of the ophidian accidents and leading to increased incidence of death. These factors, together with distribution problems, unattractive profit margins, and high costs in developing and developed countries, reduce the viability and the interest of the pharmaceutical industries in the manufacture of antivenom serums. There has been a decline in the number of producers in both private and public sectors. Chippaux provides three reasons for this dramatic reduction:

- The instability in the antivenom market;
- Little financial incentive for pharmacists and health centers to sell antivenom due to the low profit margins;
- Lack of comprehensive data on how many doses of antivenom are required and where they should be distributed.

Moreover, we must consider the supplementary therapeutic actions that a snakebite patient may require for effective treatment, such as the use of extra drugs, wound care services, reconstructive surgery, and rehabilitation therapy, all of which increase the total cost associated with it [24].

Recombinant antivenoms with oligoclonal mixes of human monoclonal antibodies are the next-generation therapy for improved treatment of snakebites. A cocktail of human antibodies is needed for efficacious and high-quality biosynthetic oligoclonal antibodies (BOA) for the treatment of snakebites. BOA cocktails include all or most of the significant toxins that are needed for the pathophysiology of snakebite. These toxins range from 20 to in excess of 40 neutralizing antibodies together with carefully selected human recombinant antibodies for a specific number of snake venoms. Depending on the specificity and number of monoclonal antibodies, BOAs can be monovalent or polyvalent. The general idea of the combination of small molecule inhibitors together with a BOA cocktail is that it could lead to improved neutralization of toxins in distal tissue by improving the pharmacokinetics. With the increased bioinformatic tools and the availability of protein structural databases, several metabolites isolated from different sources, such as plants, bacteria, fungi, and other synthetic processes, have been evaluated for

their ability to inhibit enzymes found in snake venoms. Small molecule enzyme inhibitors could provide several potential advantages; for example, serving as adjuvants and reducing the effects of intoxication while the patient is being treated in a health care center, which would increase the recovery time, thereby improving the treatment window. Furthermore, since many of these small molecule inhibitors have been evaluated for their toxicity in human receptors, they have already proven to be safe enough to be used in the treatment of snakebite envenomation [24].

Another approach for the development of snake antivenoms includes independent venom immunization techniques. There are four different strategies involved in this approach. The first strategy includes the injection of chemically synthesized epitopes of toxins, where bioinformatic software is used for the prediction of epitopes or epitope mapping studies. The second strategy involves not only the toxin epitopes but also the use of full-length recombinant or synthetic toxins as immunogens. In the third strategy, molecules with non-identical amino acid sequences that mimic the structure of the toxin epitopes, called mimotopes, are used. The final strategy involves the use of DNA, avoiding recombinant expression or chemical synthesis [24].

SPECIFICITY OF ANTISNAKEVENOMS

Absolute specificity is an issue in management with ASV. The geographic and taxonomic diversity in species leads to a significant variation in composition and antigenic reactivity of venom. So the use of a particular ASV may get restricted to a geographical area of relevant specificity. Thus, monovalent ASV would be the solution. But in view of the cost and diverse specificity, polyvalent ASV would provide answers to an extent, considering the medically important species. However, because of paucity of reliable literature on distribution and diversity of venomous species, ASV is not available for all species. This is one of the main obstacles of immunotherapy [25].

PLANTS USED AGAINST SNAKE BITE IN INDIA

- Plants reducing the symptoms. e.g. *Rauwolfia serpentina* and *Gymnemma sylvestre*
- Plants that repel snakes.e.g. Garlic and Garlic vine
- Immune system stimulants.e.g. Aristolochia species
- Plants with analgesic anti-inflammatory activity. e.g. *Rhapidophora pertusa* (Araceae) and *Azadirachita indica* [22]

PHYTOCOMPOUNDS RESPONSIBLE FOR ANTI-VENOM ACTIVITY

- Gymnemic acid (triterpenoid glycoside) from *Gymnema sylvestre* is used as a remedy for snake bite in India.
- *Eclipta prostrata* extracts inhibit effects of South American rattle snake bite. Three active compounds, coumestan, wedelolactone and sitosterol have been isolated from the crude extract of this plant.
- The tannin from *Diospyros perigrina* inhibits swelling caused by sea snake venom.
- *Curcuma longa* rhizomes (Zingiberaceae) are used to treat snake bite. Turmerone from *C. longa* afforded protection against the lethal effect of the venom of *Bothrops jararaca.*
- Atropine, from *Atropa belladona,* the deadly nightshade (Solanaceae) protects against the toxins from the green and black mamba. [22,23]

The aim of this study is to review relevant publications on anti-venom plants, some with known active molecules already isolated and explored, yet with no intention of exhausting the subject thus in this present article an endeavour has been made to explain the medicinal plants that are either used as tribal/traditional medicines or has already been proved to be useful in the treatment of venomous snakebites with a special emphasis on the isolated phytocompounds responsible for anti-venom activity.

Assessment of Anti-Ophidic Activity [4-9]

Anti-ophidic activity can be accessed by using different *in vivo* as well as *in vitro* models such as,

***In vitro* models:**

I. Phospholipase activity
II. Procoagulant activity
III. Fibrinolytic activity
IV. Proteolytic activity
V. Hyaluronidase activity

***In vivo* models:**

VI. Determination of Lethal Toxicity
VII. Haemorrhagic activity
VIII. Defibrinogenating activity
IX. Edema forming Activity
X. Myonecrotic activity

Screening of plants used in traditional medicine and determination of their active principles and different activities is being undertaken. The active principles isolated have been associated with various pharmacological properties and may provide a substantial contribution to the modern therapeutics of snake bite [25].

Anti-inflammatory activity

Ethanolic extracts of *Bixa orellana, Brownea rosa-de-monte, Dracontium croatii, Struthanthus orbicularis, Gonzalagunia panamensis*, and *Trichomanes elegans* are reported to inhibit edema due to Bothrops asper venom. Decrease of edema formation with aqueous extracts of *Casearia sylvestris* ***Sw***. has been noted in rats injected with lethal doses of Bothropic venoms. Ellagic acid has inhibited edematogenic activity due to total venom and phospholipase A2 (PLA2) from *Bothrops jararacussu*. Methanolic extract of seeds of *Vitis vinifera L*. has shown promise for the treatment of local effects of viperine bites. The extract neutralized edema-inducing property of venom. *Cordia verbenacea* extract significantly reduced paw edema, induced by *Bothrops jararacussu* snake venom [25].

Anti-hemorrhagic and anticoagulant activity

Prolongation of clotting time of blood plasma was observed with *Brownea rosa-de-monte*, *Pleopeltis percussa*, *Bixa orellana* and *Heliconia curtispatha, Trichomanes elegans*, after pre-incubation with venom. Methanolic extracts of *Mouriri pusa Garden, Byrsonima crassa Niedenzu, Davilla elliptica St. Hills* upon evaluation have shown complete neutralization of local hemorrhage. Flavonoids namely myricetin, quercetin, amenthoflavone have been attributed the antihemorrhagic potential. Quercetin is a potent lipoxygenase inhibitor. *Tamarindus indica* seed extract has neutralized the hemorrhage, indirect hemolysis and degradation of Beta chain of human fibrinogen, caused by viper venom in experimental animals. The organic acid from root extract of *Hemidesmus indicus* significantly antagonized hemorrhagic, coagulant and anticoagulant activities in experimental rodents, induced with viper venom. Lupeol acetate from the plant has neutralized hemorrhage and defibrinogen induced by Russell's Viper. Inhibition of hemorrhage and dermonecrotic activities of venoms *in vivo* is reported with methanolic extracts of leaves of *Camellia sinensis*. The action has been attributed to complexation and chelation of plant phenolic compounds and venom proteins [25].

Enzyme inhibitory activity

Enzyme inhibiting and protein binding properties have been associated with chemically active compounds of flavonoids, polyphenols, terpenoids, xanthene etc. The phytochemicals also inhibit PLA2 activities of viper and cobra venom. Phenolics, especially polyphenols, like some tannins bind proteins, acting upon components of venom directly and disabling them to act on receptors. They could also act by competitive blocking of the receptors. Tannic acid has been found to be a potent inhibitor of hyaluronidase. Inhibition of enzymatic activity is reported with extracts of *Casearia sylvestris* in experimental animals, injected with lethal doses of Bothropic venoms. Significant inhibition of PLA2 activity induced by *Bothrops pauloensis* and ***Crotalus durissus*** *terrificcus* venoms is documented with the leaf extract of *Schizolobium parahyba*. Neutralization of ***Vipera russelii*** venom enzymes namely phospholipase, protease and hyaluronidase is reported with the bark extract of ***Anacardium occidentale*** in a dose-dependent manner [25].

Antibacterial and antiparasitic activity

Mikania laevigata and *Mikania glomerata*, having antiophidian, antibacterial and antiparasitic activity, have been used in Brazil for the treatment of snake bites. A broad spectrum of antibacterial activity has been associated with root extract of *Aristolochia bracteata* in snake bites. Extracts of *Delonix elata* and *Mollugo cerviana* and *Merremia tridentata* have shown significant antibacterial activity. Medicinal properties may be attributed to bioactive compounds like alkaloids, glycosides, tannins found in these plants. They have been used for various ailments including snake bites [25].

Antimyotoxic activity

Ellagic acid from *Casearia sylvestris* aqueous extract has shown inhibition of myotoxic activity in rats when tested against effects, from both total venom and PLA2 from genus Bothrops. Neutralization of myotoxic effects of *Vipera russelii* venom is reported with the bark extract of *Anacardium occidentale*. Significant inhibition of myotoxicity induced by *Bothrops pauloensis* and *Crotalus durissus terrificcus* venoms and their isolated toxins by aqueous extract of leaves of *Schizolobium parahyba* has been documented. Methanolic extract of seeds of *Vitis vinifera* has shown neutralization of myonecrotic properties of viper venom. Edunol from Harpalyce brasiliana was found to be antimyotoxic. Myotoxicity induced by *Bothrops jararacussu* snake venom and its main PLA2 homologues is reported to be inhibited with *Cordia verbenacea* extract. Dried root extracts of *Mimosa pudica* have inhibited the myotoxicity due to *Naja kaouthia* venom. *Curcuma longa* has shown inhibition of myotoxicity due to

Naja naja venom. Partial inhibition of myotoxic activity has been reported with the *Pentaclethra macroloba* [25].

ANTIVENIN ACTIVITY

There is huge repository of medicinal plants used for treating snake bites [Table 1]. Many plants have been conserved and used as antidotes for snake envenomations. Increase in survival rates of rats has been observed with *Casearia sylvestris* extract. Different species of *Echinacea* are used in North America for treating snake bites. The plant contains echinacoside, cichoric acid, ketoalkenes, alkyl amides and polysaccharides. Anisodamine, an alkaloid isolated from *Anisodus tanguticus* with the chemical structure and pharmacological action similar to atropine and scopolamine, has been proposed to be an effective drug for snake bites [25].

Anti-venomous Plants useful in the treatment of Snakebite envenomation [1,2, 11-21]

TABLE 1 :Different Plants Reported Globally In The Snakebite Treatment

Plant	Family	Part used	Country	Reference
Humirianthera ampla	Icacinaceae	Roots	Brazil	1
Hibiscus aethiopicus	Malvaceae	Stem bark	Yemen	2
Allium cepa	Amaryllidaceae	Bulbs	Uganda	11
Vitex negundo	Lamiaceae	Leaves	India	12
Musa paradisiaca	Musaceae	Crushed stem bark	Brazil	13
Casearia sylvestris	Flacourtiaceae	Root	Brazil	14
Mucuna prurience	Fabaceae	Stem	Nigeria	15
Nectandra angustifolia	Lauraceae	Root and Seeds	Argentina	16
Strophanthus hispidus and *Strophanthus gratus*	Apocynaceae	Leaves	Ghana	17
Oxalis corniculata	Oxalidaceae	Whole plant	Colombia	18
Urera baccifera	Urticaceae	Leaf	Costa Rica	19
Zingiber officinale	Zingiberaceae	Seeds and Roots	Nicaragua	20
Dysosma pleiantha	Berberidaceae	Rhizome	Taiwan	21

Traditional concept of Snakebite and its Treatment in India

Despite the widespread success of traditional therapy, it is still important to search for other different venom inhibitors, either synthetic or natural, that could complement or substitute for the action of the traditional antivenom. Even if in a variety of cases the effectiveness of some traditional courses of therapy is not particularly apparent, conventional herbal medicine is easily available in the countryside for snakebite treatment. Some of the methods used to treat snakebites include topical application of plant leaves–juice–paste, etc.; chewing of leaves and plant parts; and drinking plant extracts or decoctions. In India as well as in other parts of the world, medicinal plants are used as antidotes for snakebites, administered either singly or in combination with other antisnake venoms or supportive plants. Thus, in the management of snakebite, the study of herbal antidotes against snake venom is of considerable significance to society [26].

Clinical complication of snake envenomation

Overall, 17·4% had early clinical complications including tissue loss associated with abscess and necrosis, acute renal failure, shock, acute lung oedema and intracranial haemorrhage. 3% had permanent sequelae, caused by muscle contractures and amputations, chronic renal failure, or death [27].

CONCLUSION

It is concluded that many evidences are available to establish the scientific background of the folklore use of plants against snake bite envenomation. Thus, medicinal plants with anti-venom activity could be considered as an effective alternative to mammalian antibody production for the treatment of snakebite envenomation. Further studies are also required not only to isolate and characterize the active chemical compounds from these plants but also their mechanism of action needs to be studied in scientific manner throughout the world to prove the clinical efficacy of claimed studies.

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