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## Snake Venom Neutralization Effects of African Medicinal Plants & Their Impact on Snakebites: A Review

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### Abstract

**Background:** Snakebite has remained an enduring medical problem for many decades and little progress has been made in reducing mortality. Globally, approximately 50,000 – 60,000 people die each year as a result of snakebite and more are left permanently impaired. Antivenom treatment is very expensive, out of reach and has several adverse effects because of the foreign proteins. Adverse effects of antivenom occur normally after one hour of administration. On the other hand, the advantages of herbal treatment are that, they are cheap, easily available, and stable at room temperature and could neutralize a wide range of venom antigen without side effects.

**Methodology:** This study was undertaken by conducting enquiries to the traditional healers and local peoples about the ethno botany used in snake bite cases. In addition, this study included the information on plants used for snake bites in other African countries.

**Conclusion:** Herbal compounds of higher plants may give a new source as different research groups are engaged not only for the discovery but possibly for discovering compounds with novel mechanisms of action that can encourage a rational approach for antivenom activity. The herbal medicines used by the traditional healers for snake bite should as much as possible be studied and decisions should be made and instructed to the traditional healers, for their safe use especially dose related problems and they should be informed to take responsibility for their own action. All these points necessitate preparing a review, exchanging the ideas, so that it can be a stepping stone and will have a great impact against snake bite treatment and management.

**Keywords:** Alternative medicines; antivenom; herbal compounds; snake bites.

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## 1. INTRODUCTION

Snakebite poisoning is an important unheeded disease in most of the developing countries. Viper snakes are among the most common types of venomous snakes which are responsible for many envenoming (Fig 1) and deaths in most tropical areas. African countries are global diversity center for feared snake families, *Vipers*, *Krait* and *Cobras*. The risk of snakebite to people in the rural region of tropical countries, where most people engage in agricultural, pastoral, and other outdoor livelihoods, is moderate to high. Snake venom (Fig 2) contains different pharmacologically active peptides and proteins. The one & only medical treatment available is the use of antisera, since 1894, but the usage of snake venom antisera has its own drawbacks. Due to its high cost & lack of availability of antisera makes it difficult for the rural patients to access. Further, due to its storage difficulty & short expiry, its use is restricted. Snake venom antiserum or AVS has administration problem, the exact dosage is also a current problem. AVS administration is often associated with hypersensitivity reactions (early & late) which need further medical attention<sup>1, 2</sup>. There are various medicinal plants which have been used in folk and traditional medicines against snakebites. But till date no such drugs are available in the market which possess anti snake venom activity. Therefore there is a need to have a scientific validation of the folk and traditional herbal medicines, as an alternative therapy in the field of snake bite management from all spheres<sup>3</sup>.

## 2. Chemistry of Snake Venom and possible mechanism

Snake venom contains different pharmacologically active peptides and proteins. Most of the proteins of snake venoms are metalloproteinases, with molecular weights ranging from 20 to 100 KDa. The high molecular weight proteinases are multimodular proteins, with a central zinc-containing catalytic domain proceeded by an N-terminal putative pro-domain and followed by a disintegrin domain and a cysteine-rich domain<sup>4</sup>. The low molecular weight proteinases consist of the highly conserved 200-204 amino acid residue catalytic domain alone, which often seems to be derived from larger precursors via post-translational proteolytic events. This catalytic domain comprises an extended HisGluXxxXxxHisXxxXxxGlyXxxXxxHis consensus sequence where x is an amino acid. Both the high and the low molecular weight forms show proteolytic activity towards various matrix proteins. Similar to the matrix metalloproteinases and to the astacins, however, their hydrolytic activity towards short peptide substrates can be extremely low; only long peptides extending three or more residues beyond the scissile

peptide bond are effectively cleaved. Snake venom metalloproteinase induce hemorrhage, local myonecrosis, skin damage, inflammatory reaction, arthritis and are responsible for causing paralysis. SVMPs also possess diverse functions such as the disruption of homeostasis mediated by procoagulant or anticoagulant effects, platelet aggregation, and apoptotic or pro-inflammatory activities.<sup>5, 6</sup> Some of the studies indicated that the mechanisms of envenoming might be contributing to the accumulation of venom proteins at the bitten area causing capillary disruption. Microscopic studies also revealed that erythrocytes are leaked through widened inter-endothelial gaps when capillaries are exposed to venomous protein. Snake venom proteins are multidomain Zn<sup>2+</sup>-dependent proteins that share structural and functional motifs with other metalloproteinases, such as matrix metalloproteinases (MMPs) and the reprotolysin family of metalloproteinase's, the 'a disintegrin and metalloproteinase'. It also contains powerful postsynaptic neurotoxins which are low molecular weight and diffuses rapidly through blood stream. It also contains toxic phospholipase A<sub>2</sub> with presynaptic neuromuscular blocking activity<sup>7</sup>.

## 3. Recent studies on snake venom neutralization by medicinal plants

Traditional medicines for snake venoms play a major role in the ability to counteract the degradation effects induced by venom toxins. It has been known for many years that animal sera and some plant extracts are competent in neutralizing snake venoms. Various plant families *viz* *Compositae*, *Leguminosae* and *Solanaceae* and *Apocynaceae* are well represented in African compendia. However, very less investigation is available on their active components isolated and characterized both structurally and functionally. Inhibitory activity of many of these plants against the snake venom enzymes has been confirmed by biological assays. Compounds present in all of them belong to chemical classes capable of interacting with macromolecular targets (enzymes or receptors). Most of the studies based on isolation of the active principle or partially purified extract reveal the presence of aristolochic acid, alkaloids, steroidal, flavanoids, phenols, pterocarpanes, quinonoid xanthenes, resveratrol, glycoside and tannins. Several studies on these herbal constituents proved the neutralization effects on viper and Russell venoms<sup>8, 9</sup>. The *H. aethiopicus* entirely (100%) blocked the haemorrhagic activity of *E. ocellatus* in the egg embryo at 3.3mg/mL of extract. This study suggests that *H. aethiopicus* may contain an endogenous inhibitor of venom-induced haemorrhage.<sup>10</sup> A. Ahmed *et. al.* (2010) studied various

crude extracts of *P. indica* for anti snake venom activity. Results of the study clearly indicating that the inhibition of platelet aggregation studies significantly decreased. The alcoholic and aqueous extracts of *P. indica*, significantly inhibited the PAL enzyme activity may be by its iteration with PAL A2 and thereby preventing hydrolysis of lecithin<sup>11</sup>.

#### 4. Medicinal plants used by traditional healers

Medicinal plants have been used for many years to treat a great variety of diseases including envenomations by animal bites. These plants play an important role in human health, as they are a good source of inhibitors and pharmacologically active compounds. Plant extracts have been shown to antagonize the activity of various

kinds of venoms and toxins. Several plant species are popularly known as anti-snake venom and have been scientifically investigated, such as, *Hibiscus esculentus*, *Casearia sp.*, *Musa paradisiaca*, *Mucuna pruriens*, *Eclipta sp.*, *Curcuma longa*, *Bauhinia forficata*, *Annoma senegallensis*, *Mikania glomerata*, *Piper sp.*, *Cordia verbenacea*, *Pentaclethra macroloba*.<sup>15, 16</sup> Generally, an aqueous, methanol or ethanol extract is prepared out of the plant part. Topical applications of the plant or its sap on to the bitten area, chewing leaves or barks or drinking extracts or decoctions or injecting the extracts are main traditional methods intended to neutralize snake venom activity (**Table 1**).

Country	Plant	Family	Local Name	Parts used / Direction
Ethiopia	<i>Cyphostemma junceum</i>	Vitaceae	Etse Zewe	Chewing roots
Ethiopia	<i>Gossypium herbaceum L.</i>	Malvaceae	Tit	Chewing root
Ethiopia	<i>Pergularia daemia L.</i>	Asclepiadaceae	Yeayit Hareg	Making small cut at location and inserting root
Ethiopia	<i>Plumbago zeylanicum L.</i>	Plumbaginaceae	Amira	Chewing Leaves
Ethiopia	<i>Verbena officinalis L.</i>	Verbenaceae	Atuch	Chewing root
Kenya	<i>Combretum molle G. Don</i>	Combretaceae	Muama, Kiama	Root or bark pounded, soaked in water and infusion drunk; 2 glasses two times a day.
Kenya	<i>Conyza sumatrensis (Retz.)</i>	Asteraceae	Yadh asere, yadh tong'	A leaf infusion of the plant is drunk as an antidote for puff adder ( <i>Bitis arietans</i> ) bites and stomachache.
Kenya	<i>Entada leptostachya</i>	Fabaceae	Mwaitha	Stem crushed, sap squeezed out and applied.
Kenya	<i>Opilia amentacea Roxb.</i>	Opiliaceae	Mutonga	Roots burnt into charcoal, crushed into powder mixed with crushed snake teeth and applied to treat the snake bites.
Kenya	<i>Solanum incanum L.</i>	Solanaceae	Mutongu	The stem or fruits cut into small pieces, dried in sun, pounded and powder applied. The sap of the fruits may also be directly applied.
Kenya	<i>Microglossa pyrifolia (Lam.) Kuntze</i>	Asteraceae	Nyabungodidi, nyabung odit	The leaves are chewed, juice swallowed and the macerate placed well into the snake bite.
Kenya	<i>Uvaria scheffleri Diels</i>	Annonaceae	Mukukuma	Information not available
Eritrea	<i>Boscia angustifolia</i>	Capparidaceae	Kermed	Root stem bark
Eritrea	<i>Nicotinia tabacum</i>	Solanaceae	Timbhako	leaves
Eritrea	<i>Solanum incanum</i>	Solanaceae	Engulle/sengol	root
Eritrea	<i>Solanum nigrum</i>	Solanaceae	Maere mtsu	Leaves/root
Eritrea	<i>Steganotaenia araliacea</i>	Umbelliferae	Mewets denagl	Stem, leaves
Eritrea	<i>Cyphostema niveum</i>	Vitacea	Information not available	Chewing Root

Table 1: Traditional medication of medicinal plants against snake bite in African countries.<sup>12, 13, 14</sup>



**Fig. 1: Venomous snake bites excruciating injuries**



**Fig. 2: Snake poison**

### **5. Conclusion and Impact on snake bite treatments**

Plants or their pure compounds and polyherb combination drug therapy is gaining popularity. This theory, though not yet implemented, must be looked into as they have low cost, less side effects, no expiry, RT-storage, local availability, easy administration & double protection in presence & absence of AVS, in snake bite management. But like all other treatments it also possesses some limitations, likely, low yield, geographical variation, toxicity, etc. Thus to conclude, there is a need to preserve the natural diversity & to

work out the mechanism of action of the above mentioned herbal compounds as to how they neutralize snake venom induced actions<sup>17</sup>. This review study revealed that there is a high diversity of medicinal plants and traditional knowledge about the use, preparation, and application which is still maintained among the peoples. On the other hand, the providers of antivenom are very unreliable and where the products are available they are very costly. The use of anti-venoms for the treatment of snake venom poisoning is

further restricted by their propensity to cause hypersensitivity reactions in sensitive patients. It is necessary to investigate, whether the mechanism of action employed in antagonizing snake venom are same as in antagonizing other systemic actions like, hepatotoxicity, anti-inflammatory, anti-oxidant, anti-cancer, etc. New plants must be continuously screened, to add on to the present knowledge on alternative medicine. Also there is a need to work on the polyherb combination drug theory (crude/ pure). A multidisciplinary approach in the field of alternative treatment, especially focusing on herbal products as in snake bite management is warranted. The knowledge and use of plants is an integral part of many ethnic rural cultures in African countries. This study was carried out basically to review the commonly used plants for the snake bite by the traditional healers in Africa and through this to document the traditional plants used by the local people. This is a humble attempt to provide a platform to all researchers whose contributions have led to an existence of such a huge ocean of knowledge on this topic. There are many areas where few things are unclearly defined, that need substantial amount of clinical research work with respect to herbals against snake bites. So, the variation of anti-venom medicinal plants in this herbal world effectively illustrates the importance of herbal medicine. At the concluding remark, the ultimate aim of health care service (traditional or modern) is to alleviate illnesses and prevent human or animal sufferings, so to achieve this goal the following recommendations are provided.

The herbal medicines used by the traditional healers for snake bite should as much as possible studied and decisions should be made and instructed to the traditional healers, for their safe use especially dose related problems and informed to take responsibility for their own action. There should be a rigorous effort to collect the data about the various medicinal plants

having effect in snake bite used by the traditional healers.

The systematic phytochemical and pharmacological investigation will definitely lead to the identification of the plants which could be useful as medicinal agents for snake bite treatment. The government should encourage and give incentives for the stronger side of the traditional healers rather than criticizing the traditional medication as a whole as inferior and ineffective.

This will motivate the traditional healers to share their knowledge with the emerging generations.

## 6. Summary

Antivenom treatment is very expensive, out of reach and has several adverse effects because of the foreign proteins. Adverse effects of antivenom occur normally after one hour of administration. On the other hand, the advantages of herbal treatment are that, they are cheap, easily available, and stable at room temperature and could neutralize a wide range of venom antigen without side effects. This study was undertaken by conducting enquiries to the traditional healers and local peoples about the ethno botany used in snake bite cases. In addition, this study included the information on plants used for snake bites in other African countries. Herbal compounds of higher plants may give a new source as different research groups are engaged not only for the discovery but possibly for discovering compounds with novel mechanisms of action that can encourage a rational approach for antivenom activity. All these points necessitate preparing a review, exchanging the ideas, so that it can be stepping stone and will have a great impact against snake bite treatment and management.

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