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Review Article

ANTISNAKE VENOM PROPERTIES OF MEDICINAL PLANTS

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ABSTRACT

Snake envenoming and consequent deaths are of common occurrence in tropical and subtropical regions. Approximately 1,25,000 deaths are witnessed every year and WHO has declared it as a neglected tropical disease in 2009. The immunotheraphy is the only treatment available, but it has side effects like serum sickness, pyrogen reactions moreover the non availability and storage problems has rendered the mankind to look in others sources to treat snake bite deaths. This has led to the investigation of naturally available antidotes or the herbal antidotes. The plants were used by humans from centuries to treat diseases which have become an ancient knowledge which are passed through the generations. Many scientific investigations have been carried out on the grounds of folk knowledge. Some of the plants include *Aristolochia indica*, *Andrographis paniculata*, *Hemidesmus indicus, Vitis vinifera etc.,* many metabolites have also been isolated which show promising pharmacological inhibitory effect on the toxic snake venom. Further exploration and characterization of molecules would be able to provide an alternative to the existent Antisnake venom.

Keywords: Snake bite, Antisnake venom, Herbal remedies, Folk medicine.

INTRODUCTION

The word "Snake" has fascinated humankind for years and evokes either a positive or a negative response. The mere interest about the species is due to the physiological effect of their venom on the prey such as paralysis, myonecrosis and often death [1]. Ophidian envenomation or snake bite is a neglected public problem in both tropical and subtropical countries where rural populations are most affected. South East Asia is the most affected region in the worldwide with its dense population and more agricultural practices. In 2009 WHO declared the snake bite as one of the neglected tropical conditions [2].

Worldwide 2650 advanced species of snakes were found and are categorized into *Viperidae*, *Elapidae*, *Atractaspididae* and *Colubridae* families. In India alone more than 60 species of venomous snakes were found among them spectacled cobra (*Naja naja*), common krait (*Bungarus caeruleus*), saw-scaled viper (*Echis carinatus*) and Russell's viper (*Daboia russelii*) have long been recognized as the medically important Big-Four snakes [3]. Some of the important snakes in India (table 1).

The true number of deaths due to snakebite has been documented as 54,00,000 bites with 2,50,000 envenomations and 1,25,000 deaths annually throughout the world among them India reporting higher mortality rates. Most snake bite and related deaths occur in Asia, southeast and Sub-Saharan Africa with India reporting the highest mortality. It has been reported in India alone 81,000 snake bites and 11,000 deaths occur per year [4].

In 1869 Joseph Fayrer quantified the first human snakebite deaths for about half of "British India" where 11,416 had died due to snake bites [5]. Further reports of human deaths due to snakebite before Indian Independence was between 7,400 to 20,000 per year [6-8]. Government of India has reported that there were 61,507 snake bites and 1124 deaths in 2006, 76,948 envenomations and 1359 deaths in 2007 [9]. Indian government hospitals reported only 1,364 deaths in 2008 [10]. These reports believed to be under reported as the number of people visiting the hospitals are not accurate. These differences in estimates have concluded that annual snakebite mortality in India varies from approximately 1,300 to 50,000. A National survey has reported about 45,900 deaths in India alone with Andhra Pradesh having highest mortality rate [11].

Table 1: Important poisonous snakes of India

Family	Common name
Viperiadae	
• *Daboia russelli*	Russell's viper
• *Echis carinatus*	Saw scaled or carpet viper
• *Hypnale hypnale*	hump-nosed viper
• *Trimeresurus gram ineus-*	Indian bamboo pit viper
Elapidae	
Cobra:	
• *Naja naja*	Common spectacle Indian cobra
• *N. Koauthia*	Monocellate cobra
• *N. oxiana*	North Indian cobra
• *Ophiophagus hannah*	King cobra
Krait:	
• *Bungarus caeruleus*	Common krait
• *B. fasciatus*	Banded krait
• *B. sidanus wall*	Wall's sind krait
• *B. niger*	Black krait

The present review is to provide an outline regarding the statistics of snake bite deaths, antivenom availability and its management, alternative therapy and herbal antidotes which offer an alternative to the available treatment which has been used by ethnic groups and also under scientific investigation.

Snake venom

The most poisonous and complex of all natural venoms are snake venoms [12,13]. The venom of any nature possess many varieties of toxic and non-toxic proteins, peptides, and also non-protein toxins, carbohydrates, lipids, amines, and other small molecules. The toxins of most importance in human envenoming include those that affect the nervous, cardiovascular, and haemostatic systems, and cause tissue necrosis [14]. The composition of the snake venom varies according to its habitat within the species. It is varied based on diet, age, season. This variation may be responsible for the complexity in the venom. The elapid and viperid venoms comprise 25-70% and 80-90% of enzymes respectively.

The most common enzymes in snake venoms are phospholipase A_2 (PLA_2), serine proteinases, metalloproteinases, acetylcholinesterases (AChEs), L-amino acid oxidases, 5' nucleotidases, phosphodiesterases, phosphomonoesterases and hyaluronidases. Some venom (Russell's Viper) also possess that activate factors V, X, IX and XIII, fibrionlysis, protein C, anticoagulation.

Phospholipase A2 is the most widespread venom that causes damage to the red blood cells, leucocytes, mitochondria, skeletal muscle, nerve endings. Hyaluronidase helps in the spreading of the venom from the bite site to other tissues. The acetylcholinesterase present in most elapids causes paralysis [15].

Antivenom

The only treatment to the snake bite is antibodies obtained from an animal that has been injected with the venom [16]. In 1895 Albert Calmette produced the first anti venom against *Naja naja* and was readily accepted [17]. In India polyvalent antivenom are produced against the "Big Four" medically important snakes by immunizing horses with their venom. India has about seven pharmaceutical companies which produce the ASV.

Even though the ASV is been produced in India for 100 years the potency of it has deterred compared to 1950's. The main concerns are ideal storage conditions (4ºC), affordability, transportation and more importantly the specificity. There is a huge variation in the species of a particular snake which restricts the usage of the ASV with regard to a geographical area [18].

The unavailability of snake venom has resulted in the underproduction of ASV, furthermore the lyophilization is a costly process and there are possibilities of physiochemical changes in the lyophilized form. The liquid form requires cold storage [19] and can be stored only upto 2 years. Along with it the ASV is associated with many side effects like anaphylaxis, pyrogen reactions and serum sickness. It may induce early or late adverse reactions [20] (table 2).

Table 2: Adverse reactions of antivenom

Reactions	Effects
Early reactions (anaphylactic reactions) (developed after 10-180 min after administration)	Urticaria, itching, tachycardia, vomiting, Abdominal colic, headache, Minor cases have fatal anaphylaxis–brochospasm, hypotension, angioedema
Pyrogen reactions (developed after 1-2 hrs after administration)	Fever, rigor, chill and low blood pressure
Late reactions (serum sickness) (developed in 1-12 days of therapy)	fever, nausea, vomiting, arthralgia, arthritis, diarrhea, itching, recurrent urticaria, mayalgia, lymphadenopathy, proteinuria, neuritis and even encephalopathy

Herbal remedies

Plants and their molecules in addition to the therapeutic use as folk medicine also have contributed to the production of the number of drugs which are still in use like vincristine, an antitumour compound, morphine, rutin, a potent vasodilator. Molecules that are of medicinal interest are often present in lower amounts in plants due to seasonal variations, time of the collection, growth stage, climate, soil variability and also the part from which the molecules are extracted. Some are available in abundant amount which are directly manufactured and used as medicines. A world market produces US$ 320,000,000/year turnover from pharmaceutical products out of which US $ 20,000,000 are vegetal sources. The last years have seen an increase in demand for the exploration of the medicinal plants to extract molecules for therapeutic uses [21].

The non availabilty of medical facilities to treat snake envenomations have led to the exploration of plant resources which provide an alternative to the immunotherapy. The ancient ayurvedic system of India refers to the usage of plants in management of snake envenomation, along with it Atharva veda, Rig veda, Charaka and Sushruta samitha also mentions about the various plants used in this regard [18].

Many traditional healers in remote areas have treated people with this ancient knowledge. Some of the plants which possess the metabolites to neutralize the pharmacological activities of the snake venom would be further looked for antivenin activity [22].

The plant kingdom possesses enormous resources which are exploited by tribals in India. Many studies on various plants have been carried out based on the information available with the tribals to treat snake bite. This has led to various studies and some of the active principles have also been isolated. Many plants have been exploited for their pharmacological potential on the four medically important snakes of India (table 3).

Table 3: Summary of inhibition of pharmacological activities of Indian snakes

Plants	Snake	*In vitro* inhibitory activity	Hemolytic inhibitory activity	Anti hemorrhagic activity	Anticoagulant activity	Antimyotoxic activity	Anti edema forming activty	Reference
Acorus calamus	*Echis carinatus*	+	-	-	+	-	+	[23]
Acalypha indica	*Vipera russelli*	-	+	+	-	-	-	[24]
Anacardium occidentele	*Vipera russelli*	+		+	+	+	+	[25]

Andrograph-is paniculata	*Naja naja*	+	+	-	-	-	-	[26]
	Daboii Russelli	+	-	+	+	-	+	[27]
Aristolochia indica	*Daboii Russelli*	+	-	+	+	-	+	[27]
Aristolochia bracteolata Lam	*Vipera russelli*	+	-	+	-	-	-	[28]
	Naja naja	+	-	+	-	-	-	
Caltopis gigantea	*Vipera russelli*	-	-	+	-	-	+	[29]
Cordia macleodii	*Naja naja*	-	-	+	+	-	+	[30]
Crescentia cujete	*Vipera russelli*	-	-	+	-	-	-	[31]
Emblica offincialis	*Vipera russelli*	+	-	+	+	-	-	[32]
	E. Carinatus	+	-	+	+	-	-	
	Naja naja	+	-	-	+	-	-	[33]
Hemidesmus indicus	*Vipera russelli* *Echis Carinatus*	-	-	+	+	-	-	[34]
Leucas aspera S	*Vipera russelli*	+	-	-	-	-	+	[28]
	Naja naja	+	-	-	-	-	+	
Magnifera indica	*Vipera russelli*	+	-	+	+	+	+	[35]
Mimosa pudica	*Vipera russelli*	+	-	+	+	-	+	[36]
	Echis carinatus	+	-	+	+	-	+	
	Bungarus caeruleus	+	-	+	+	-	+	[37]
	Naja naja	+	-	+	+	-	+	
Mucuna pruriens	*Naja naja*	+	-	+	+	-	+	[38]
	Bungarus caerleus	+	-	+	+	-	+	
Piper longum	*Vipera russellii*	-	-	+	-	-	+	[39]
Pluchea indica	*Vipera russelli*	+	-	+	+	-	-	[32]
	E. Carinatus	+	-	+	+	-	-	
Strynchous nux-vomica	*Vipera russelli*	+	-	+	-	-	-	[40]
Symplocos cochinchinensis (Lour.) S. Moore ssp. *Laurina*	*Vipera russellii*	-	+	-	-	-	-	[41]
Tamarindus indica	*Vipera russellii*	+	+	+	+	+	+	[42]
Tylophora indica (Burm. f.) Merrill	*Vipera russelli*	+	-	-	-	-	+	[28]
	Naja naja	+	-	-	-	-	+	
Vitis vinifera	*E. carinatus*	-	-	+	+	-	+	[43]
Vitex negundo	*Vipera russelli*	+	+	-	+	-	-	[44]
Withania somnifera	*Naja naja*	+	-	-	-	+	+	[45]
	Echis carinatus	+	-	-	+	-	+	

Azima tetracantha Lam	*Vipera russelli*	+	-	-	-	-	-	[46]
	Bungarus Caeruleus	+	-	-	-	-	-	
Abutilon indicum	*E. carinatus*	+	-	-	-	-	-	[47]
Carisssa spinarum Linn	*Vipera russelli*	+	-	-	-	-	-	[48]
	Bungarus Caeruleus	+	-	-	-	-	-	
Tabrnaemon-tana	*E. carnitus*	+	-	-	-	-	-	[49]
alternifolia	*Naja naja*	+	-	-	-	-	-	
Rauwolfia	*Naja naja*	+	-	-	-	-	-	[50]
serpentina	*Daboia russelli*	+	+	-	-	-	-	[51]
Allium sativum	*Naja naja*	+	-	-	+	-	-	[33]
Ocimum sativum	*Naja naja*	+	-	-	+	-	-	
Azadirachta indica	*Naja naja*	+	-	-	+	-	-	

(-= not determined)

Several studies indicate plants crude extracts showing inhibitory effects and some by isolated compounds. A very few compounds have been isolated whose molecular structure are also been characterized (table 4). In many places where plants are used to treat ophidian envenomation, some of them are inactive in pharmacological and scientific investigations.

Guerranti *et. al.,* has isolated some proteins from seed extract of *M. prureins* which has inhibited the toxic effects of *E. carinatus* [52]. A glycoprotein inhibitor of 27kDa was isolated from *Withania somnifera* that has resulted in effectively neutralizing the PLA2 activity of cobra and viper venom [53].

It also inhibited the hyaluronidase activity completely in viper and cobra venom [45]. A peptide RW 12 has shown anti cobra activity isolated from *Schumanniophyton magnificum* [54].

A multiform glycoprotein isolated from seed extract of *M. pruriens* has indicated to play a key role in producing immunological protection against the snake bite in victims. Lupeol acetate isolated from the roots of *Hemidesmus indicus* has inhibited the PLA2 activity of Russell viper [55]. Aristolochic acid from *Aristolochia radix* has inhibited the enzymatic and pharmacological activities of Phospholipase A2 of *Vipera russelii* [56]. Poly phenols derived from *Areca catechu L* showed inhibition of enzymes against *Naja naja kouthia* [57]. Pentacyclic triterpenes, betulin and betulinic acid were isolated from *Betula alba* have shown inhibitory activity against PLA2 [58]. Potassium salt of gymnemic acid has inhibited the ATPase activity of *Naja naja* venom [59]. 2-hydroxy-4-methoxy benzoic acid isolated form *Hemidesmus indicus* has shown antisnake venom activity in experimental models. It increased the venom neutralization along with the antiserum and reducing the free radical scavenging activity [60, 61].

Table 4: Some of the isolated compounds with anti ophidian activity

Plant species	Isolated compound
Mikanaia glomerata [20]	Coumarin
Hemidesmus indicus[55,60]	2-hydroxy-4-methoxy benzoic acid, lupeol acetate
Cynara scolymus[20]	Cynarin
Cordia verbenacea[62]	Rosmarinic acid
Eclipta prostrata[63]	Wedelolactone, Sigmasterol, D-mannitol
Eclipta protrata[20]	Demethylwedelolactone
Silybum marianum[20]	Sillymarin
Tabrnaemontana catharinensis[64]	12-methoxy-4-methoxy voachalotine
Aristolachia sp. [56]	Aristolochic acid
Mimosa pudica[20]	D-mannitol, sitosterol
Mucuna pruriens[65]	gpMuc
Strychnos nux vomica[20]	Amide
Piper caldense[20]	Caldensin
Withania somnifera[66]	WSG
Curcuma longa[67]	Ar-tumerone
Casearia sylvestris[68]	Ellagic acids
Betula alba[58]	Betulin, betulic acid
Pluchea indica[69]	B-sitosterol, sigmasterol

Anti-thrombotic properties were observed *in vivo* with Glycyrrhizin, a molecule isolated from the roots of *Glycyrrhiza glabra* which also prevented the venom-induced changes in hemostasis, both *in vivo* and *in vitro* [70]. A molecule similar to atropine and scopolamine has been isolated from *Anisodus tanguticus* called has been proposed to be an effective drug for snake bites [71].

CONCLUSION

Snake bite has resulted in high mortality especially in rural areas. A policy needs to be implemented to provide the ASV to the rural parts of India. Due to the diversity of species it is difficult to develop a species specific immunotherapy which has resulted to look for alternative sources.

The herbal antidotes provide an arena to explore since they are abundant, easily available in remote places as well. Hence the need to investigate the metabolites present in the plants based on the knowledge of ancient culture and traditional practices has risen exponentially. Many studies have been carried out in this regard and few novel compounds are also been isolated. Still many compounds and resources need to be studied to isolate an antivenin that can replace the ASV.

CONFLICT OF INTERESTS

Declared None.

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