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Snake Bite in India: Current Scenario of an Old Problem

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Abstract

Snake bite is a significant health concern, especially in rural populations of tropical and subtropical countries. In India, snake bites take a heavy toll of human lives, and therefore warrant urgent attention. High mortality is due to poor health services in rural areas and delay in getting the victim to a well-equipped health care facility, where anti snake venom can be administered. However, geographical and species variation, logistic, economic and production issues restrict the use of anti-snake venom. India has a large repository of medicinal herbs, which have been used in folk medicine for treatment of snake bites. Though numerous herbal remedies are scientifically unsubstantiated, yet they cannot be glossed over due to their inherent advantages. They are practiced by diverse social groups for long, offering unconditional benefits. In view of limited presence of modern medical avenues in far flung areas, such a resource needs to be harnessed, as herbals are cheap, acceptable and often at the disposal of victims. Exhaustive ethno botanical studies in different regions of the country can help to undertake well designed scientific studies, for establishing therapeutic efficacy of various herbals for treating snake bites. The present article highlights an assortment of herbal plants used in India for snake bites.

Keywords Snake bite; Mortality; Therapeutic efficacy

Introduction

Snake bite is a neglected public health problem in tropical and subtropical countries, where rural populations are mainly affected. It is a common occupational hazard mainly in farmers, plantation workers, herders and laborers leading to significant morbidity and mortality that remains largely unreported. The bites inflicted are frequently accidental as when snakes are trodden upon or could result due to sleeping on floor and open style habitation. The most affected region in the world is South East Asia because of dense population and extensive agricultural practices. The WHO has included snake bite in its list of neglected tropical conditions in 2009 [1].

The true global burden of snake bite is not known due to lack of standardized reporting and underreporting. It is documented that there are 54,00,000 snake bites with 2,50,000 envenomations and around 1,25,000 fatalities annually in the world. Most snake bites and fatalities occur in Asia, Southeast, and sub-Saharan Africa, with India reporting the highest mortality due to snake bites [2]. However, there is no accurate statistics of morbidity and mortality, which could certainly be higher, because most of the victims initially approach traditional healers for treatment and are not even registered in the hospital.

India is reported to have the highest number of snake bites (81,000) and deaths (11,000) per year [2]. However, the geographical distribution and statistics are variable in the country due to gross underreporting, resulting in massive statistical disparity. Estimates of death due to snake bite range widely from 1,300-50,000. According to Government of India data, there were 61,507 snake bites with mortality of 1124 in 2006; 76,948 bites and 1359 deaths in 2007. A high mortality of 50,000 deaths each year has also been published [3]. In the state of Maharashtra an average of 1,224 deaths per year (2.43 deaths per 1,00,000 per year) were reported between 1974 and 1978. Random community based surveys in some localities in West Bengal, have shown much higher annual mortality rates of 16.4 deaths per 1,00,000 [4]. A report by the hospitals of Government of India, from all states, except six documents just 1,364 deaths due to snakebites in 2008, believed to be gross under reporting, as rural victims seek traditional treatment [5]. A nationally representative snake bite mortality survey in India (2001-2003) has highlighted 45,900 deaths annually, with the highest mortality rate in the state of Andhra Pradesh [6].

Fatality due to snake bite is due to wide species variation, shortage of anti-snake venom (ASV), poor compliance with treatment protocols, lack of public education and clear policy to deal with the problem. There is relative paucity of credible information on snakes and on dealing with emergencies in case of snake bite. Reliance on traditional healers and myths further compound the problem. However, high death count cannot be ascribed to superstition and lack of awareness only, because there are a number of victims who die after seeking medical attention, the reason being lack of experience in handling such cases and non-compliance with the existing guidelines.

Snake bite is a common medical emergency, where timely treatment can reduce morbidity and mortality and save precious human lives. Lack of information about simple measures of prevention, occupational hazard risks and inappropriate first-aid measures all magnify the risk. Poor access to health care services, difficult transportation and consequent delay in ASV administration result in high fatality. The time elapsed after the bite is of vital importance, because with the passage of time more venom gets bound to the tissues and is thus less manageable for neutralization by ASV. Further, use of ASV may be avoided due to inexperience and fear of anaphylaxis or it may be administered irrationally when not indicated at all, resulting in wastage of resources and exposing the patient to toxicity risk of high doses. Moreover there is a lot of uncertainty in the doses of ASV, though National Protocol on Snake Bite Management formulated by

the Ministry of Health & Family Welfare, Government of India is in place besides the WHO Guidelines [3,7].

Further, the peripheral health care facilities are not well equipped and there is shortage of ASV, emergency drugs, ventilators etc thus necessitating a trip to well equipped tertiary care hospitals, where treatment may be unaffordable due to limited purchasing power of the rural victims. High mortality can be attributed to loss of crucial golden hour and lack of treatment.

The organized effort to cope with important aspects of snake bite management is inadequate; foremost being the first-aid management of the patient and prompt medical management of emergencies especially in rural areas. A lot of precious time is lost in travelling to the nearest medical facility leading ultimately to morbidity and mortality.

To overcome the hurdles of non availability of ASV in remote areas and sometimes its ineffectiveness because of species specificity, herbal remedies are preferred. Moreover most of the victims especially in rural areas lose precious time by attending traditional healers and quacks.

The present review is an attempt to sketch a resume of the current prevailing problem of snake bite, the management of envenomation, use and obstacles of immunotherapy, herbal antagonists and promising alternative option provided by various medicinal plants, which have been extensively used by ethnic groups in India to treat snake bites.

Common poisonous snakes in India

There are nearly 3150 species of snakes in the world and around 600 species are venomous [8]. In India, out of the 216 species of snakes, 60 are considered poisonous [9]. The most poisonous, medically important species of India distributed widely throughout the country, include Cobra, Common Krait, Russell's viper and Saw-scaled viper. There are other venomous snakes also which are variedly distributed throughout the country (Table 1).

Family	Snake species	Common name	Geographical distribution in India
Elapidae	Naja naja	Common spectacled Indian cobra	Throughout
	Naja kaouthia	Monocellate cobra	Northeast
	Naja oxiana	North Indian or Oxus cobra	Northwest
	Naja sagittifera	Andaman cobra	Andaman islands
	Ophiophagus hannah	King cobra	South, Northeast, Andaman islands
	Bungarus caeruleus	Common krait	Northeast
	Bungarus fasciatus	Banded krait	Northwest
	Bungarus niger	Black krait	
	Bungarus sindanus	Sind krait	
Viperidae	Daboia russelii	Russell's viper	Southwest
	Echis carinatus	Saw-scaled viper	Southwest
	Echiscarinatus sochureki	Sochureki's saw scaled viper	Northwest
	Hypnale hypnale	Hump-nosed pit viper	Southwest coast and Western Ghats
	Cryptelytrops albolabris	White-lipped tree viper	East
	Cryptelytrops purpureomaculatus	Mangrove pit viper	East
	Trimeresurus malabaricus	Malabar pit viper	Southwest
	Trimeresurus gramineus	Indian bamboo viper	South, Andaman and Nicobar islands
	Macrovipera lebetina	Blunt-nosed viper	Northwest

Table 1: Poisonous snakes of India and geographical distribution.

The hump-nosed pit viper identified recently is documented to be responsible for nearly 10% of venomous bites in the state of Kerala [10,11]. Areas like far northeast, the Himalayan region and the Andaman and Nicobar islands have distinctive herpeto fauna.

The venom glands in Elapids and Viperids are present behind the eye and are surrounded by compressor muscles. They inject venom into the prey by fangs which are modified teeth. While in Elapids, the short fangs are mounted on a relatively fixed maxilla in front of the mouth, in Viperids the long fangs are mounted on a rotatable maxilla, facilitating flat folding against the roof of the mouth. A subfamily of vipers called the Crotalinae comprises of pit vipers. They have a special sense organ situated between the nostril and the eye to detect their warm-blooded prey. In humans, snakes usually inject venom subcutaneously or intramuscularly and the average dry weight of venom injected at a strike is approximately 60 mg (*N. naja*), 13 mg (E. carinatus) and 63 mg (D. russelii) respectively.

Snake Venom

Snake venom is a highly complex cocktail of proteins, peptides, non protein toxins, carbohydrates, lipids, amines and other molecules. The chemical composition of venom varies at all taxonomic levels. Further, composition can vary considerably between snakes in different geographical locations and individuals within those populations. The composition is also subject to change based on diet, age, season and environment. The widely differing manifestations of snake bite could be attributed to complexity of venom to some extent.

The snake venom mainly contains proteins (>90%, dry weight). There are more than hundred different proteins in each venom; with

elapid and viperid venoms constituting 25-70% and 80-90% of enzymes respectively. Some non-enzymatic polypeptide toxins and non-toxic proteins are also present [3].

The snake venoms are mainly characterized as neurotoxic and hemotoxic. The neurotoxic venoms act at molecular level, by disrupting the neuromuscular junctions, limiting muscle activity while hemotoxic venoms cause tissue destruction in body systems besides their effect on circulatory system.

The venom enzymes include hydrolases, hyaluronidase, kininogenase. Other enzymes include phosphomono-and diesterases, 5'-nucleotidase, DNAase, NAD-nucleosidase, l-amino acid oxidase, phospholipase A2(PLA2), peptidases and zinc metalloproteinase hemorrhagins. Blood clotting may be stimulated by serine proteases and other pro-coagulant enzymes present in some Elapid and Viperid venoms. Certain venoms contain toxins (Russell's viper) that activate factors V, X, IX and XIII, fibrinolysis, protein C, platelet aggregation, anticoagulation and hemorrhage.

Widespread damage to mitochondria, red blood cells, leucocytes, platelets, peripheral nerve endings, skeletal muscle, vascular endothelium, and other membranes is caused due to phospholipase A2, the most widespread enzyme present in the venom. Hyaluronidase aids in venom dissemination from the bite site through tissues.

Most elapid venoms contain acetylcholinesterase, which could cause tetanic paralysis. Among the polypeptide toxins are postsynaptic (α) neurotoxins that bind to acetylcholine receptors at the motor endplate. Presynaptic (β) neurotoxins release acetylcholine at the nerve endings at neuromuscular junctions and damage the endings, interfering with its release [3].

Antisnake venom

The most effective antidote against snake venom is the anti snake venom. It is usually pepsin refined F (ab) fragments of IgG purified from the serum or plasma of a horse or sheep that has been immunized with the venom of one or more species of snakes. ASV neutralizes the venom of a particular species (monovalent/ monospecific) or various different species (polyvalent/polyspecific). The antibodies against a particular species may also neutralize the venom of a closely related species (paraspecific activity). In India, horses are hyper immunized against the venom of four common poisonous snakes the "Big Four" (Cobra, Krait, Russell's viper and Saw-scaled viper), to produce polyvalent anti snake venom. The venom is mostly procured from Chennai in South India. There are seven pharmaceutical laboratories in India that produce ASV against four medically important Indian snake species [12].

Management of Snake Envenomation

In India, the high morbidity and mortality due to snake bites could be attributed to traditional, harmful first-aid measures like application of tight tourniquets, cutting, suction, cryotherapy, application of herbal and folk medicines and above all the usual delay in carrying the patient to the nearest health care facility and providing appropriate medical care. In view of multiple treatment modalities followed by treating physicians in the country, the Ministry of Health & Family Welfare, Government of India has drafted the National Snake Bite Management Protocol to provide guidelines for proper management of snake bites [7]. Taking lead from National Guidelines, the locally developed protocol in West Bengal, upon implementation has shown less number of deaths and an overall reduction in ASV usage [13].

The foremost thing for a bitten victim is reassurance and immobilization with a splint or a sling followed by lightly wrapping a bandage. If possible identification of the snake and exact time of bite may help in determining the progression of impending neurotoxic or hemotoxic effects.

A brief history of the bite and the progression of local and systemic symptoms and signs is mandatory. The management in hospital involves the care of airway, breathing, circulation and shock. Examination of local signs and symptoms like fang marks, local pain, swelling, bleeding from the site, blister formation etc can also give some clues about the species of biting snake. Hemostatic abnormalities may be ascribed to vipers and neurotoxic manifestations principally to cobras and kraits. However, Russell's viper in certain areas of India may also cause neurotoxic symptoms believed to be due to presynaptic toxin. Hump-nosed pit viper and Russell's viper cause renal failure. The necessary investigations include the 20 WBCT and usual hematocrit, biochemistry and arterial blood gases.

The corner stone of management is administration of ASV which is raised against the four common species of snakes found in India. ASV is given only in patients with evidence of systemic envenoming (coagulopathy, neurotoxicity) or severe local envenomation. Generally administration of 8-10 vials of ASV is recommended and further dosing depends on response to the initial dose [7]. For victims, reporting late after several days, the presence of coagulopathy or neurotoxic symptoms determines the ASV administration. The current venom activity determines the administration of ASV, as only unbound venom can be neutralized. A number of methods including ELISA have been developed for detection of venom and antibodies. Species specific ELISA aids in diagnosis, and subsequent management as it helps in identifying the exact species of snake, monitoring the circulating venom antigen and hence the dose of ASV. Since snake identification is generally not easy and the presentation can always be confusing, because of overlapping of symptoms, venom and antibodies detection in blood can be helpful. The adverse reactions are usually managed with antihistamines, adrenaline and late serum sickness with prednisolone and antihistamines.

Antisnake venom: The issues

There are some critical issues with ASV, the production of which started 100 years ago in India. The potency of the presently available ASV is less than what it was prior to 1950's. The main issues with ASV in actual clinical practice are species specificity, difficulty in availability, affordability and ideal storage conditions. One of the principal drawbacks of the immunotherapy is the issue of specificity. There is a huge species variation with current taxonomy identifying one, four and eight species of Russell's viper, cobras and kraits, respectively. Two subspecies of saw-scaled vipers have also been identified. Russell's viper venom has also shown regional variation [12]. So the variable composition and antigenic reactivity of the venom restricts the use of a particular ASV to a geographical area with relevant specificity. Moreover, ASV cannot be raised against all species because the literature on distribution and diversity of venomous species is scarce. The concept of "Big Four" restricts the development of an effective ASV. Venom variation, low potency, bites by other species could be responsible for the reported failure of polyvalent ASV in countering the venom effects in India.

Further there are various logistic, marketing and economic issues with the production and supply of ASV. Though India spearheaded the manufacturing of low cost ASV, the supply has been disrupted due to closure of manufacturing facilities resulting in acute shortage. Undersupply of the venom is the main cause of insufficient production of ASV to meet the national requirement. The process of development is time consuming, requiring ideal storage conditions. Production in lyophilized form is costly, and there can be physiochemical changes in the product by lyophilization. The liquid form requires cold chain. The production of monovalent ASV is a costly affair. In India the monovalent ASV is not produced. However, it has been proposed that in developing countries, the production of ASV can be sustained at affordable prices if cost efficient methods of production are kept in mind. There needs to be rapid technical advancement in production [14].

The other drawbacks with ASV therapy are the adverse reactions ranging from early reactions (pruritus, urticaria) to potentially fatal anaphylaxis. Few cases may also develop serum sickness. Endotoxin contamination could also lead to pyrogen reactions.

Herbals: A Possible Choice

Due to inadequate health care facilities especially in rural areas of India, people largely depend on alternative treatment by traditional healers who have knowledge based on ancient culture, ethnic practices and herbal antidotes. The plant kingdom provides an inexhaustible source of various herbal compounds with pharmacological potential which hold the key to antivenin activity [15]. A plethora of medicinal plants, available locally are used widely by traditional healers. Numerous traditional and folk medicines in the form of plant sap, pastes, decoctions, powders and pills are used by traditional healers for treating snake envenomations. Description of various types of snakes, use of various medicinal herbs and treatment modalities has been extensively discussed in Ayurveda. Treatment in Ayurvedic texts has been classified into Chaturvimashi upkramas with modalities like Mantram (chanting of mantras) and Arishta bandhanam (application of tourniquets). However ambivalence in approach is observed when compared with present day medical science. Though the modalities are debatable, yet they could be useful in remote areas [16].

The plant kingdom has tremendous resources which have been thoroughly exploited by ethnic tribes in India. There are numerous studies highlighting use of various plants by different ethnic groups for treating snake bite in different parts of India [17-29]. Leads from ethnic groups, have led to isolation and characterization of novel, pharmacologically active principles which have been used in snake bites (Table 2).

Plant	Active principle	Enzyme inhibitory activity	Anti-hemorrhagic activity	Anti-inflammatory activity	Anti-coagulant activity	Anti-bacterial activity	Anti-myotoxic activity	Region of ethnosocial use (ref)
Andrographis paniculata	Terpenoids	+	-	+	-	-	-	AndhraPradesh [17,21,22] Tamilnadu [25,26], Arunachal Pradesh [27]
Areca catechu	Polyphenols Quercitin, Curcumin, Tannic acid	+	+	-	-	-	-	Tamilnadu [28]
Aristolochia sps.	Aristolochic acid	+	-	-	-	-	-	Andhra Pradesh [17,21] Karnataka [19] Tamilnadu [25,26,27] Madhya Pradesh [27]
Azadirachta indica	AIPLAI	+	-	-	-	-	-	Tamilnadu [26]
Eclipta prostrata	Wedelolactone, D-mannitol, Sitosterol, Stigmasterol	-	+	-	-	-	-	AndhraPradesh [17] Tamilnadu [25,26]
Emblica officinalis	Phthalate Triterpenoids	+	+	+	-	-	+	Maharashtra [27]
Gymnema sylvestre	Triterpenoid glycoside	+	-	-	-	-	-	Madhya Pradesh [20]
Hemidesmus indica	2-hydroxy-4-methoxy benzoic acidLLupeol acetate	+	+	+	+	-	-	Andhra Pradesh [17] Madhya Pradesh [20] Chattisgarh [23] Tamilnadu [25,26] West Bengal [27]
Macuna pruriens	Glycoproteins	+	-	+	+	-	-	Andhra Pradesh [[17] Chattisgarh [23] Tamilnadu [26] Uttar Pradesh [27]

Mimosa pudica	Tanins	+	+	+	+	-	+	Andhra Pradesh [17] Karnataka [[19] Madhya Pradesh [20, Chattisgarh [23] Tamilnadu [26,27] Uttar Pradesh, Nagaland [27]
Morus alba	Prenylflavanes Glycoside	+	+	+	+	-	-	Tamilnadu [29]
Strychnos nux vomica	Amide, Caffeic acid, SNV NF	+	+	+	-	-	-	Andhra Pradesh [17,22] Tamilnadu [25] Orissa [27]
Vitex negudo	Triterpenoids	-	+	+	+	-	-	Himachal Pradesh, Karnataka, Kerala [27]
Withania somnifera	Alkaloids, Glycoprotein WSG	+	-	-	-	-	-	Karnataka [19,27]

Table 2: Plants with pharmacological potential used for treating snake bites

Various phytochemicals with enzyme inhibiting and protein binding properties, active against snake envenomations include flavonoids, polyphenols, saponins, tannins, terpenoids, xanthenes etc. Phenolics, especially polyphenols, like some tannins bind proteins and act directly on venom components. They could also competitively block the receptors. Flavonoids like myricetin, quercetin, amenthoflavone have antihemorrhagic poteintal.

Ursolic acid commonly found in many medicinal plants has enzyme inhibitory activity [30]. Gallic acid (3,4,5-tri-hydroxy benzoic acid), on testing against the local toxicity of *Daboia russelli* venom and its purified hemorrhagic complex, showed inhibition of in-vitro proteolytic activity of both venom and hemorrhagic complex, without inhibiting phospholipase activity of venom. In-vivo experiments, showed inhibition of hemorrhage, edema forming, dermo- and myonecrotic activities of both the venom and the complex [31]. 2-hydroxy-4-methoxy benzoic acid, salicylic acid and p-anisic acid have shown neutralization of phospholipase A2 activity of banded krait, which was superior to ASV neutralization. A combination of the ASV and herbal compound has been suggested to be more useful [32].

Salireposide and benzoylsalireposide, phenolic glycosides from *Symplocos racemosa* are documented to possess venom inhibitory activity [33]. The terpenoids from the plant have antiproliferative effects and certain phenolic glycoside derivatives have demonstrated enzyme inhibitory activity against venom [34]. Triterpenoids from the root extract of Emblica officinalis and *Vitex negundo* are suggested to significantly neutralize the venom induced effects of Vipera russelii and Naja kauothia [35].

There is a huge collection of Indian medicinal plants used for treating snake bites. Some of the important plants with experimentally proven antivenom activity are discussed below:

Hemidesmus indicus

Antisnake venom activity has been shown in experimental models with 2-hydroxy-4-methoxy benzoic acid, isolated from Hemidesmus indicus. Increased neutralization of lethal action of venom by polyvalent antiserum has been reported with the compound in experimental models. It has also shown potentiation of antiserum action and reduction in venom induced free radical generation [36,37]. The hemorrhagic, coagulant and anticoagulant activities induced with viper venom in experimental rodents were significantly antagonized by the organic acid from the root extract [38]. Neutralization of edema induced by Russell's viper, and cardiotoxicity, neurotoxicity and respiratory changes induced by Naja kaouthia venom in experimental animals has been reported with lupeol acetate found in the plant. It also significantly neutralized PLA2 activity induced by Russell's viper [39].

Tamarindus indica

The plant has shown potent venom neutralizing properties. Myotoxic effects due to Russell's viper have been significantly neutralized with the extracts of Tamarindus indica. Early effects of envenomation by Russell's viper; inflammation, local tissue damage, and hypotension have been inhibited by the seed extract of the plant, in a dose dependent manner. Preincubation of venom with different doses of seed extract before assays, has shown significant neutralization of edema [40].

Vitis vinifera

The seed extract has been found to be useful for neutralization of various venom induced activities. Local effects of viper bites can be treated with methanolic extract of seeds of *Vitis vinifera*. Neutralization of edema inducing and myonecrotic properties of venom has been shown with the extract. The seed extract is reported to abolish enzyme inhibition (hyaluronidase, proteolytic activities), neutralize hemorrhage and cause partial inhibition of pro-coagulant activity due to viper venom [41].

Aristolochia sps. (A. indica, A. bracteata, A. radix)

The extract of A. indica is reported to have strong gelatinolytic, collagenase, peroxidase and nuclease activities along with l-amino acid oxidase and protease inhibitory potencies. It has been proposed that topical application of the extract may give some relief from snake bite due to strong inhibition of l-amino acid oxidase [42]. The enzymatic and pharmacological activities of PLA2 induced by Vipera russelii

venom are documented to be inhibited by aristolochic acid from *A. radix* [43,44]. The root extract of A. bracteata is reported to have antibacterial activity [45]. A significant anti inflammatory activity has been shown with the extract of A. indica [46].

Strychnos nux vomica

The plant contains caffeic acid and monomeric caffeic acid. It is used by tribals for snake bites and has anti inflammatory activity [47]. The plant is reported to effectively neutralize viper venom lethality. The seed extract has anti hemorrhagic potential and viper venom induced lipid peroxidation in experimental animals is reported to be inhibited with seed extract [48].

Andrographis paniculata

The plant extract has shown antivenin activity in experimental animals [49]. Inhibition of toxic enzymatic effects of Echis carinatus is documented with the plant extract of Andrographis paniculata. Inhibition of PLA2 and neutralization of procoagulant activity has been observed with the extract. The plant has shown significant anti inflammatory activity [46].

Withania somnifera

A glycoprotein isolated from the plant has been found to be effective in cobra and viper bites. Inhibition of hyaluronidase activity due to venoms of Naja naja and *Daboia russelii* is documented with the glycoprotein isolated from the plant [50].

Morus alba

The extract of the plant is effective against the venom of Daboia russelii venom. The leaf extract has been documented to neutralize hyaluronidase activity, edema, myonecrotic activity and also cause partial inhibition of procoagulant activity [51].

Curcuma longa

Turmerin isolated from the plant has shown inhibition of edema due to Naja naja venom. The plant has effectively countered the myotoxic activity due to Naja naja venom [52].

Eclipta prostrata

The main constituent of the plant, demethylwedelolactone is reported to cause partial inhibition of hemorrhagic activity [53].

Mimosa pudica

The dried root extracts have shown inhibition of myotoxicity due to Naja kaouthia venom [54]. The plant is also reported to have antihyaluronidase activity against Naja naja, Vipera russelii and Echis carinatus venoms [55]. The aqueous extract of dried roots is associated with significant inhibitory effect on lethality, inflammation, phospholipase, hemorrhagic and fibrinolytic activities due to Naja naja and Bangarus cearulus venoms [56].

Anacardium occindentale

The extract of the bark is associated with anti inflammatory activity and also neutralized myotoxic effects due to Vipera russelii. The extract has shown enzyme inhibition in a dose dependent manner [57].

Azadirachta indica

A significant inhibition of PLA2 enzymes of cobra and Russell's viper venoms has been reported with leaf extract of Azadirachta indica containing the active compound AIPLAI [58].

Gymnema sylvestre

Inhibition of ATPase induced by Naja naja venom is reported with a triterpenoid saponin from the plant [59].

Ehretia buxifolia

The root bark of the plant is documented to have antisnake activity Ehretianone, a quinonoid xanthenes, is the active compound isolated from the plant [60].

Areca catechu

The plant contains polyphenols. In-vivo tests with polyphenols of Areca catechu and Quercus infectoria are documented to cause inhibition of the hemorrhagic activity of Calloselasma rhodostoma venom and dermonecrotic activity of Naja kauothia venom [61].

Crocus sativus

An improvement in venom induced oxidative stress, hematological alteration and proinflammatory cytokine levels have been reported with Crocus sativus [62].

Cardiospermum halicacabum

An isoquinoline alkaloid, berberine, isolated from the plant is a potent natural inhibitor of phospholipase A2 [63].

Pluchea indica

B-sitosterol and stigmasterol from the root extract have been proposed to help in neutralization of venom induced effects along with antiserum [64].

Emblica officinalis

The plant has been established to have enzyme inhibitory, anti hemorrhagic, anti inflammatory and anti myotoxic potential in experimental models [65].

Macuna pruriens

The plant contains glycoproteins. Neutralization of edema, PLA2, hemorrhagic, fibrinolytic and procoagulant activities has been shown with the plant extract [66].

Significant antibacterial activity has been associated with extracts of Delonix elata, Mollugo cerviana and Merremia tridentate [67]. Neutralization of coagulant, fibrinolytic and phospholipase activities is documented with extracts of Emblica officinalis, Azadirachta indica, imum sanctum and Allium sativum [68]. Snake venom neutralization has been associated with leaf extract of Acalypha indica [69]. Use of Costus speciosus roots containing diosgenin and starch in the rhizome has also been documented [70]. Root extract of Ophiorrhiza mungos

has shown potent anti snake venom activity against Russell's viper in experimental models [71]. Further, there are a number of studies that highlight the use of various herbs for treating snake bites in different parts of the country [25,60,72-76] (Table 3).

Plant used	Active principle
Achyranthes aspera	Glycosides, oleanolic acid
Allium cepa	Quercitin, sulfurous volatile oils, oleanolic acid, protocatechuric acid
Amaranthus spinosus	Oleanolic acid, α-spinosterol, saponoside
Argemone mexicana	Alkaloids, tannins, terpenoids, flavonoids
Bryophyllum pinnatum	Alkaloids, triterpenes, glycosides
Ehretia buxifolia	Ehretianone, α-amyrin
Enicostemma axillare	Tannins
Glorosia superba	Esters
Ipomoea digitata	Triterpenoids, flavonoids
Pimpinella anisum	Anisic acid
Rauwolfia serpentina	Alkaloids
Salix alba	Salicylic acid
Tephrosia purpurea	Alkaloids, flavonoids, saponins, tannins, triterpenoids
Trichosanthes tricuspidata	Trichotetral, cucurbitasne glycosides, cucurbitacins

Table: 3 Plants with antivenin activity.

Conclusion

Snake bite should be declared a notifiable disease. A National policy should be formulated and implemented to ensure prompt availability and effective use of ASV in the rural areas of the country. Training of treating physicians and knowledge of protocols to deal with emergencies should be mandatory and Government should ensure availability of ASV.

However, development of species specific ASV is an enormous challenge because of species diversity in India. In view of various obstacles of immunotherapy, a growing dependence on natural resources is imperative. The reliance on herbal medicines is vitally important because of wide acceptance, easy availability, affordability, safety, cultural preference, and chiefly the poor health care services in rural areas. So the importance of traditional medicines cannot be underscored.

Nature provides a huge armamentarium for treating snake bites. The pharmacological potential of very few plants has been investigated so far. There are still numerous unidentified novel compounds which may have antivenin activity or supplement the action of anti snake venom. Though vital leads have been provided by ethnic groups and helped in exploring the antivenin properties of plants, but well designed and validated scientific studies are required to establish their therapeutic effectiveness in snake envenomations.

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