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Anti-snake venom properties of medicinal plants

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ABSTRACT

Snake venom has been the cause of innumerable deaths worldwide. Many people die every year in India alone. For the last century, antiserum is the only available specific treatment. However, antiserum does not provide enough protection against venom induced haemorrhage, necrosis, nephrotoxicity and often develops hypersensitivity reactions. India has a rich tradition of the usage of medicinal plants. Many Indian medicinal plants are mentioned in literature, which are used to treat snakebite victims especially in the rural areas. However, only a few species have been scientifically investigated and still less had their active components isolated and characterized both structurally and functionally. This article presents a review of plants showing neutralizing properties against snake venoms which were assayed in research laboratories, correlating them with ethnopharmacological studies. So plant remedies may be beneficial for the treatment of snakebite and may find alternative to antivenom serum.

Keywords: Plant extracts, Anti-snake venom, Ethnopharmacology, Biological activity

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INTRODUCTION

Snakebites represent a public health hazard that leads to high morbidity and mortality in the Indian subcontinent [1]. Conservative sources estimates that the number of accidents globally reaches one million, resulting 600,000 evenomations and more than 20,000 deaths annually [2]. Other sources place annual incidences globally at 5 million with about 40,000 or more deaths – close to 10% mortality attributed to malaria [3]. In India alone more than 200,000 cases are reported and an estimated 35,000 to 50,000 people dies each year [4].

Antiserum is the only therapeutic agent available throughout the world. Antivenom is made by immunizing mammals such as horse, goat, rabbit with particular snake venom and the specific immunoglobins are isolated from the blood [5-6]. Snake venoms are complex mixture of

enzymatic and toxic proteins, which include phospholipase A2 (PLA2s), myotoxins, hemorrhagic metalloproteinases and other proteolytic enzymes, coagulant components, cardiotoxins, cytotoxins and neurotoxins [7-9]. Traditional herbal medicine is readily available in rural areas for the treatment of snakebite. Plants are used either single or in combination, as antidotes for snake envenomation by rural populations in India and in many parts of the world. Plants are reputed to neutralize the action of snake venom, with a plethora of plants claimed to be antidotes for snakebites in folk medicine [10]. This review is an attempt to focus on the plant based treatment of snakebite, using information related to ethnopharmacology and in-vivo experimental models.

Type of Venomous snake

Ophitoxaemia is the rather exotic term that characterizes the clinical spectrum of snake bite envenomation. Of the 2500–3000 species of snakes distributed worldwide, about 500 are venomous. Based on their morphological characteristics including arrangement of scales, dentition, osteology, mycology, sensory organs etc., snakes are characterized into families. The families of venomous snakes are Atractaspididae, Elapidae, Hydrophidae and Viperidae. The major families in the India subcontinent are Elapidae which includes common cobra, king cobra and krait, Viperidae which includes Russell's viper, pit viper and saw-scaled viper and Hydrophidae (sea snakes) [11]. Of the 52 poisonous species in India, majority of bites and consequent morbidity is attributable to 5 species viz. *Ophiophagus Hannah* (king cobra), *Naja naja* (common cobra), *Daboia rusellii* (Russell's viper), *Bungarus caeruleus* (krait) and Echis carinatae (saw-scaled viper) [12].

Clinical Complications of Snake envenomation

Envenoming by snakes is responsible for several clinical complications of severe systemic and local pathology. For example, *E. ocellatus* causes swelling, blistering, and necrosis and haemorrhages due to both metalloproteases and ecarin (an enzyme which activates prothrombin) [13-14]. While envenoming by *Naja n. nigricollis* leads to local necrosis, haemorrhage, complement depletion and respiratory arrest or paralysis [15-16]. Its venom consists of PLA2s (an anticoagulant enzyme which inhibits the prothrombinase complex by its binding to coagulation factor Xa) and cardiotoxin [17-19]. In some cases envenoming can induce corneal ulceration and anterior uveitis [20-21]. In human accidents, *Bothrops* venoms cause local tissue damage, as well as hemorrhage, proteolysis, myonecrosis and edema. Muscle necrosis is an important local effect induced by several snake venoms, sometimes resulting in an irreversible loss of tissue and occasionally requiring amputation of the affected limb. Myonecrosis may be due to an indirect action as a consequence of vessel degeneration and schemia caused by hemorrhagic metalloproteases or by a direct effect of myotoxic PLA2s homologues upon plasma membranes of muscle cells [22,9].

Limitations of antisnake venom therapy

Antivenom immunotherapy is the only specific treatment against snake venom envenomation. There are various side effects of antivenom such as anaphylactic shock, pyrogen reaction and serum sickness. Most of these symptoms may be due to the action of high concentrations of nonimmunoglobulin proteins present in commercially available hyper immune antivenom [23]. Although an intravenous administration of antivenom, prepared from IgG of venom-immunised horses or sheep, is an effective treatment for systemic envenoming the clinical consensus is that

antivenom is of limited effectiveness against the effects of local envenoming that develop rapidly after a bite [24-25]. Such effects include severe pain, oedema, localized haemorrhage, and necrosis. Which often results in permanent scarring and deformity [26].

Ethnobotanical for the treatment of snakebite (India)

In India, there are about 54 million indigenous people of different ethnic groups inhabiting various terrains. These indigenous groups possess their own distinct culture, religious rites, food habit and a rich knowledge of traditional medicine. Even today, indigenous and certain local communities practice herbal medicine to cure a variety of diseases, with plants particularly used as folk medicine to treat snakebites. Numerous plant species are used as folk medicine for treatment of snake-bite are summarized in Table 1. Topical application of plant extracts on bitten area, chewing leaves or barks, drinking or injecting extracts, can counteract snake venom activity.

Table 1. Traditional plants used against snakebite (India)

Plant species	Family	Parts used	Direction	Administration
Abrus precatorius	Leguminosae	Roots	Unknown	Oral (5 days)
Abutilon indicum	Malvaceae	Leaf, Fruits	Leaf juice mixed with jaggery	Oral (2days)
Acacia leucophloea	Mimosaceae	Bark	Bark paste	External (1 Week)
Acalypa indica	Euphorbiaceae	Leaf	Paste	External (3–4 days)
Achillea millefolium	Asteraceae	Whole plant	Paste	Oral (6 days)
Achyranthes aspera	Amaranthaceae	Leaf, Stem	Paste	External (3 Weeks)
Acorus calamus	Araceae	Rhizome	Paste	External (7 days)
Aegle marmelos	Rutaceae	Root bark	Water Decoction	Oral (2 Weeks)
Aerva lanata	Amaranthaceae	Rhizome	Unknown	Oral (11 days)
Alangium salvifolium	Alangiaceae	Root bark	Decoction	Oral(twice a day up to 4 days)
Allium cepa	Liliaceae	Skin bulb	Paste	External application (5 days)
Andrographis paniculata	Acanthaceae	Whole plant	Decoction, Paste	Internal/External (5–14 days)
Andrographis lineata	Acanthaceae	Leaf Flower	Juice	Oral (5 days)
Argemone mexicana	Papaveraceae	Leaf Seed	Decoction	Oral (7 days)
Aristolochia indica	Aristolochiaceae	Root	Paste	External (1 Week)
Azadirachta indica	Meliaceae	Flower	Decoction	Oral (7 days)
Caesalpinia bonduc	Caesalpiniaceae	Seeds	Paste	External (2 Weeks)
Calendula officinalis	Asteraceae	Flower	Juice	Oral (4 days)
Calotropis gigantean	Asclepiadaceae	Root	Paste with ghee	Oral (3–7 days)
Cassia alata	Caesalpiniaceae	Leaf	Paste	Oral (21 days)
Cassia tora	Caesalpiniaceae	Leaf	Decoction	External (14 days)

Citrus limon	Rutaceae	Ripe skin	Paste	External (3 days)
Clinacanthus mutans	Acanthaceae	Leaf	Paste	External (7 days)
Curcuma longa	Zingiberaceae	Rhizome	Paste	External (3 Weeks)
Cymbopogon citrates	Poaceae	Whole plant	Fresh plant	Repel snakes (Night)
Cyperus rotundus	Cyperaceae	Rhizome	Decoction	Oral (7 days)
Dalbergia melanoxylon	Fabaceae	Stem bark	Decoction	Oral (6 days)
Eclipta alba	Compositae	Whole plant	Paste	Oral (14 days)
Eclipta prostrata	Compositae	Leaf	Paste	External (21 days)
Ehretia buxifolia	Ehretiaceae	Root	Paste	External (7 days)
Euphorbia hirta	Euphorbiaceae	Whole plant	Decoction	Oral (5 days)
Erythrina excelsa	Fabaceae	bark	Juice/paste	Both (3–7 days)
Feronica limonia	Rutaceae	Root	Juice	Oral (3 days)
Gloriosa superba	Liliaceae	Tuber	Paste	External (2–5 days)
Gymnema sylvestre	Asclepiadaceae	Root	Tincture	Oral (4 days)
Glycine max	Leguminosae	Seeds	Juice	Oral (Week)
Helianthus annuus	Asteraceae	Seed	Oil	External (14 days)
Hemidesmus indicus	Asclepiadaceae	Root	Decoction	Oral (7 days)
Tragia involucrate	Euphorbiaceae	Whole plant	Juice	Oral (6 days)
Morus alba	Moreaceae	Leaf	Juice	Oral (3 Weeks)
Leucas cephalotes	Lamiaceae	Leaf	Past/Juice	Oral (Twice a day for 6 days)
Madhuca longifoila	Sapotaceae	Nut	Paste	External (2–3 days)
Mimosa pudica	Mimosaceae	Whole plant	Paste	External (5 days)
Momordica charantia	Cucurbitaceae	Flower	Paste with olive oil	External (3 days)
Moringa oleifera	Moringaceae	Bark Root	Tincture	External (3 days)
Musa paradisiaca	Musaceae	Skin bark	Juice	Both (Week)
Nicotiana tabacum	Solanaceae	Leaves	Decoction	Oral (3 days)
Nerium oleander	Apocynaceae	Seeds	Paste	External (14 days)
Ocimum basilicum	Lamiaceae	Whole plant	Decoction	Oral (Week)
Ocimum sanctum	Lamiaceae	Leaf	Juice	Oral (8 days)
Oldenlandia diffusa	Rubiaceae	Whole plant	Paste	External (21 days)
Oldenlandia umbellate	Rubiaceae	Leaf Root	Paste	External (14 days)
Ophiorrhiza mungos	Rubiaceae	Root	Juice	Oral (Twice a day for 6 days)
Phyllanthus emblica	Euphorbiaceae	Fruit	Juice	Oral (14 days)
Phyllanthus niruri	Euphorbiaceae	Flower	Paste	External (21 days)
Phyllanthus reticulates	Euphorbiaceae	Leaf	Infusion	Oral (7 days)
Piper nigrum	Piperaceae	Flower	Paste with ghee	Oral (4 days)
Pluchea indica	Asteraceae	Seed, flower	Paste/Juice	Internal/external (7 days)
Punica granatum	Punicaceae	Whole plant	Paste	External (12 days)
Rauvolfia serpentina	Apocynaceae	Root	Unknown	External (10 days)

Sapindus emarginatus	Sapindaceae	Bark	Paste	Oral (5 days)
Semicarpus anacardium	Anacardiaceae	Root	Unknown	Oral (7 days)
Solanum torvum	Solanaceae	Flower	Paste	External (8 days)
Strychnos nux-vomica	Loganiaceae	Stem bark	Paste	External (12 days)
Syzygium cumini	Myrtaceae	Stem bark	Decoction	Oral (14 days)
Teprhosia purpurea	Leguminosae	Root	Decoction	Oral (7days)
Thymus vulgaris	Lamiaceae	Whole plant	Juice	Oral (14 days)
Terminalia arjuna	Combretaceae	Bark	Paste	External (5 days)
Trichodema zeylanicum	Boraginaceae	Root	Aqueous extract	Oral and External (3 days)
Tylophora longifolia	Asclepiadaceae	Leaf Flower	Unknown	Unknown
Vitex negundo	Verbenaceae	Leaf	Paste	External (5 days)
Wedelia calendulae	Asteraceae	Leaf	Juice	Internally (14 days)

***In-vivo* plant extracts activity against snake venom**

Natural inhibitors of snake venoms play a significant role in the ability to neutralize 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. The purpose of this review is to highlight the recent work that has been accomplished with natural inhibitors of snake venoms as well as revisiting the past research including those found in plants. The biomedical value of these natural inhibitors can lead to the development of new therapeutics for an assortment of diseases as well as contributing to efficient antivenoms for the treatment of ophidic accidents. Most recent work has been carried out with mice for the testing of total crude extracts and is summarized in Table 2. The venom dose is important factor, on which the herbal constituents could show their neutralizing effects. There are various mechanisms by which snake venom neutralization occur such as protein precipitation, enzyme activation, chelation, adjuvant action, antioxidant, protein folding and many more.

Table 2. Investigated plant extracts activity against snake venom

Snake species	**Plant (Family)**	**Part**	**Extracts**	**References**
Viper russelli	*Acalypha indica* (Euphorbiaceae)	Leaves	Methanol	[27]
Naja naja	*Alocasia cucullata* (Araceae)	Roots	80% ethanol	[28]
Naja naja, Daboia russelli	*Andrographis paniculata* (Acanthaceae)	Herb	90% ethanol, Methanol	[29-30]
Naja nigricotlis	*Annona senegalensis* (Annonaceae)	Rootbark	Methanol	[31]
Bothrops jaracaca	*Apuleia leiocarpa* (Leguminosae)	Roots	Water	[32]
Naja naja	*Aristolochia sp.* (Aristolochiaceae)	Roots	Ether, Methanol	[33]
Bothrops asper	*Asclepias curassavica* (Apocynaceae)	Leaves		[34]

Bothrops jaracaca	*Bredemeyera floribunda* (Polygalaceae)	Roots	Water	[32]
Bothrops atros	*Brongniartia podalyriaides* (Leguminosae)	Root	Petrol-methylene chloride	[35]
Bothrops jaracaca	*Brunfelsia unifora* (Solanaceae)	Leaves	Water	[32]
Bothrops asper	*Buddleja nitida* (Scrophulariaceae)	Leaves	-	[34]
Bothrops jaracaca	*Casearia sylvestris* (Fiacourtiaceae)	Seeds	Water	[32]
Bothrops asper	*Cedrela tonduzii* (Meliaceae)	Leaves, stems	-	[34]
Bothrops asper	*Citharexylum macrodenium* (Verbenaceae)	Leaves	-	[34]
Bothrops asper	*Croton draco* (Euphorbiaceae)	Stems	-	[34]
Bothrops jaracaca	*Chiococca brachiata* (Rubiaeeae)	Roots	Water	[32]
Echis ocellatus, Bitis arietans and Naja nigricollis.	*Crinum jagus* (Amaryllidaceae)	Bulb	Methanol	[36]
Bothrops jaracaca	*Cynara scolymus* (Compositae)	Leaves	Water	[32]
Echis carinatus	*Diodia scundens* (Rubiaceae)	Aerial part	95% ethanol	[37]
Laticauda semifasciata	*Diospyros kaki* (Ebenaceae)	Fruits	Tannin	[38]
Bothrops jaracaca	*Dorstenia brasiliensis* (Moraceae)	Roots	Water	[32]
Crotaius durissus, Calloselasma rhodostoma	*Eclipta prostrata* (Asteraceae)	Herb	Ethanol, Butanol	[39,40]
Echis carinatus	*Ehretia buxifolia* (Boraginaceae)	Rootbark	Methanol	[41]
Bothrops jaracaca	*Elephantopus scaber* (Compositae)	Leaves	Water	[32]
Vipera russellii and Naja kaouthia	*Emblica officinalis* (Euphorbiaceae)	Roots	Methanol	[42]
Vipera sp.	*Geranium sp.* (Geraniaceae)	Herb	Water	[43]
Bothrops jaracaca	*Harpalyce brasiliana* (Fabaceae)	Roots	-	[44]
Daboia russellii, Naja kaouthia	*Hemidesmus indicus* (Asclepiadaceae)	Roots	Methanol	[45]
Echis ocellatus, Naja	*Hibiscus aethiopicus*	Herb	Water	[46]

n. nigricollis	(Malvaceae)			
Bothrops alternatus	*Lychnophora pinaster* (Asteraceae)	leaves	Dichloromethane, ethanol	[47]
Bothrops alternatus	*Mandevilla velutina* (Apocynaceae)	Roots	Water	[48]
Bothrops jaracaca	*Marsypjanthes hyptoides* (Labiatae)	Herb	Water	[32]
Bothrops jaracaca	*Mikania glomerata* (Compositae)	Leaves	Water	[32]
Naja naja kaouthia	*Mimosa pudica* (Mimosaceae)	Herb	Water	[49]
Bothrops jaracaca	*Morus Alba* (Moraceae)	Stems and leaves	-	[50]
Echis carinatus, Naja hannah	*Mucuna pruriens* (Papilionacee)	Seeds	Water	[51]
Bothrops jararacussu and *Bothrops neuwiedi*	*Musa paradisiaca* (Musaceae)	Stem	Juice	[52]
Naja nigricollis and Echis ocellatus	*Parkia biglobosa* (Mimosaceae)	Stembark	Methanol /Water	[53]
Bothrops jaracaca	*Penellia ternate* (Araceae)	Rhizome	-	[54]
Bothrops jararacussu	*Pentaclethra macroloba* (Mimosaceae)	Bark	Water	[55]
Bothrops jaracaca	*Periandra mediterranea* (Leguminosae)	Roots	Water	[32]
Bothrops jaracaca	*Periandra pujalu* (Leguminosae)	Roots	Water	[32]
Bothrops asper	*Persea americana* (Lauraceae)	Seeds	-	[34]
Bothrops jaracaca	*Phyllanthus klotzschianus* (Euphorbiaceae)	Leaves	Water	[32]
Bothrops asper	*Platymiscium pleiostachyum* (Fabaceae)	Leaves	-	[34]
Naja naja	*Picrasma quassioides* (Simaroubaceae)	Leaves	Water	[56]
Naja melanoleuca, Naja kaouthia	*Schuanniophyton magnificum* (Rubiaceae)	Rootbark	Water	[57,58]
Bothrops jaracaca	*Stachytarpheta dichotoma* (Verbenaceae)	Herb	Water	[32]
E. carinatus	*Strophanthus sp.* (Apocynaceae)	Leaves	Water	[59]
Bothrops asper	*Struthanthus orbicularis* (Loranthaceae)	Leaves	Ethanol	[60]

B. jararacussu, B. moojeni, B. alternatus,	*Scleria pterota* (Cyperaceae)	Leaves	-	[61]
Viper russelli	*Tamarindus indica* (Leguminosae)	Seed	95% Ethanol	[62]
Bothrops jaracaca	*Wilbrandia ebracteata* (Cucurbitaceae)	Roots	Water	[32]
Naja naja	*Withania somnifera* (Solanaceae)	Roots	-	[63]
Daboia/viper russelli	*Vitis vinifera* (Vitaceae)	Grape Seeds	Methanol	[64]
Bothrops jaracaca	*Vernonia condensata* (Compositae)	Leaves	Water	[32]
Vipera russellii, Naja kaouthia	*Vitis negundo* (Verbenaceae)	Roots	Methanol	[42]

Phytoconstituents active against snake envenomation

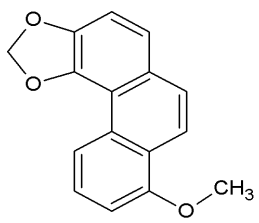
Plant compounds have played important role in the development of an impressive number of novel synthetic drugs. The compound isolated from plant species, having antiophidian properties are lised in Table 3. The phytochemicals such as plant phenols, alkaloid, triterpenoid, steroid showed effective antisnake venom activity are given in Figure 1.

Table 3. List of isolated constituent with Antiophidian activity

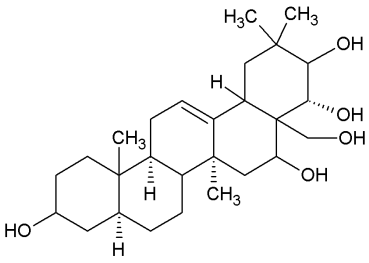
Isolated constituent	Plant	Antiophidian activity	References
Anisodamine	*Anisodus tanguticus*	Cholinergic receptor blocking agents	[65]
Aristolochic acid	*Aristolochia* sp	Anti- PLA2 activity	[66]
Clerodane diterpenoid	*Baccharis trimera*	Anti-proteolytic and anti-hemorrhagic properties	[67]
Betulin and betulin acid	*Betula alba*	Anti- PLA2 activity	[50]
Bredemeyeroside D	*Bredemeyera floribunda*	Anti-lethal activity	[68]
Edunol	*Brongniartia Podalyrloides*	Anti-lethal activity	[54,35]
Rosmarinic acid	*Cordia verbenacea*	Anti- PLA2 activity	[69]
Cynarin	*Cynara scolymus*	Anti-lethal activity	[70]
Ehretianone	*Ehretia buxifolia*	Anti-lethal activity	[41]
Wedelolactone	*Eclipta prostata*	Anti-myotoxic, anti-hemorrhagic activity	[71,39]
Tannins	*Guiera senegalensis*	Anti-lethal activity	[72]
2-hydroxy-4-methoxy benzoic acid	*Hemidesmus indicus*	Anti-lethal activity, anti-hemorrhagic activity, coagulant, defibrinogenating, fibrinolytic activity	[73]

Edunol	*Harpalyce brasiliana*	Anti-Myotoxicity,	[74]
D-mannitol, sitosterol	*Mimosa pudica*	Anti-proteolytic, anti-hyalurnidase, anti-lethality, antimyotoxicity	[75,76]
Steroids	*Mandevilla velutina*	Anti-PLA2	[43]
4-nerolidylcatechol	*Piper umbellatum, Piper peltatum*	Anti-PLA2, anti-myotoxic	[77]
Benzoylsalireposide salireposide	*Symplocos racemosa*	Anti-Phosphodiesterase I	[78]
Amide	*Strychnos nux vomica*	Anti-lethal activity, Anti-hemorrhagic, defibrinating, Anti- PLA2 activity	[79]
Flavonoids	*Sapindus saponaria,*	Hemorrhagic activity	[32]
Caffeic acid and derivatives Chlorogenic acid	*Vernonia condensata*	Antidotes	[80]

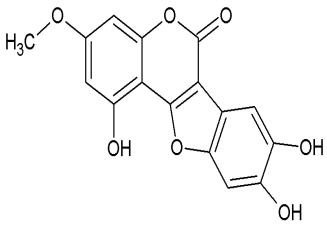
Figure 1. Phytoconstituents active against snake envenomation



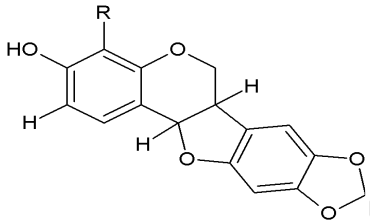
Aristolichic acid



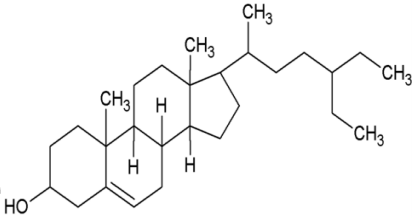
Gymnemic acid



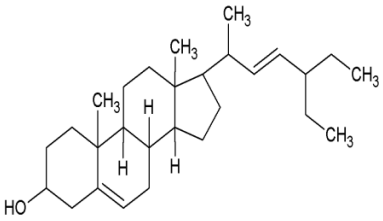
Wedelolactone



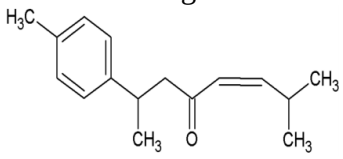
Cabenegrin-I



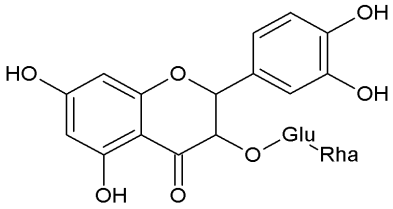
Stigmasterol



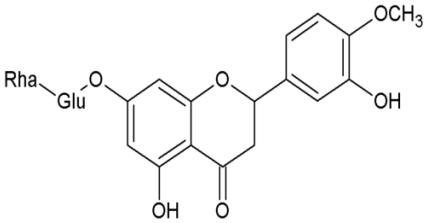
Sitosterol



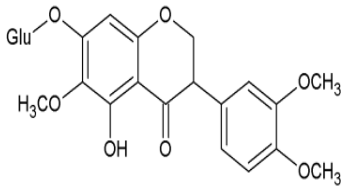
Ar-turmerone



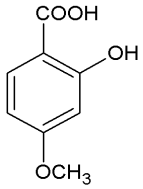
Rutin



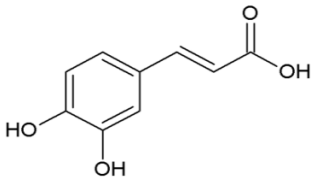
Hesperidin



Iridin



2-Hydroxy-4-methoxy benzoic acid



Caffeic acid

Tests for detection of snake venoms, toxins and venom antibodies

Identification of the biting species of a snake by the victims is usually difficult and clinical manifestations alone are not reliable because of overlapping symptoms. Detection of snake venom and venom antibodies in bodyfluids plays an important role in the management of snake envenomation. Bioassays, immunodiffiusion, immunoelectrophoresis, immunofluoresence, haemagglutination, radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA) etc. have been developed for venom detection, and ELISA is used for venom antibody detection.[81] ELISA appears to be the ideal method for both venom and venom antibody detections [82-84]. Species diagnosis is made difficult by the many venomous species present within some geographical region and also by the presence of cross-reacting venom antigens. Lack of specific immunoreagents, low level sensitivity, lengthy incubation steps and the need for expensive equipment have hampered the widespread use of routine diagnostic methods such as RIA and ELISA during the early 1980s. However, significant progress has been made during the last ten years to develop species-specific ELISA for the detection of venoms/toxins in various parts of the world, particularly in developing countries where the snake bite is a major medical and social problem. Hybridoma technology and affinity chromatography have been adequately utilized to develop species-specific immunoreagents for diagnostic purposes.

CONCLUSION

The usage of natural medicine has been influenced by inadequacy of biomedical health system, and due to its costeffectiveness and cultural acceptability. In India, the rural areas are most affected by snake envenomation and medicinal plants have been widely used as a remedy for treating snakebite [1,27]. Ethnic groups from these zones use herbal remedies against envenomation without antivenom administration and it is the accepted therapy in these places. Plant extracts represent an extremely rich source of pharmacologically active compounds and possess more than one biochemical/pharmacological property. Interaction of such compounds with the toxins/enzymes leads to the neutralization/inhibition of their activities. So plant remedies may be beneficial for the treatment of snakebite and may find alternative to antivenom serum.

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