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Innovation development and standardization of Novel Herbal Formulation

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A review on herbs against snake venom

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Abstract

Snakebite is major problem still depending on treatment of antisera as though they have their own limitations. Hence this review concentrates on elaborating various herbs and herbal antidotes that can be used against snake bites. Such components can help overcome the limitations of anti-venoms as they are naturally obtained. Herbs can also be easily available and quickly given to victims. Also, they are cost effective as compared to anti-venoms. Various parts of the plants such as roots, rhizomes, leaves, fruits, seeds and their extracts can be utilized to neutralize the snake venom of various snake species. There are various evident Anti-Venom limitations that can interfere with the efficiency of the anti-venom. This article covers the list of some species of the plants which counteracts selective snake's venoms. There is detailed specification of herbs related to their origin, the venom of snake it acts on, dose and other related parameters.

Keywords: Snakebite, Snake Poison, Herbs, Herbal constituents, Snake venom treatment

Introduction

Snake Poisoning is considered as a serious health hazard which affects the people vastly. Exact epidemiology of snake poisoning cases are overall less. Out of the total poisonous species of snakes, majority of species responsible for poisoning are *Ophiophagus hannah* (King Cobra), *Naja naja* (spectacled cobra), *Daboia russelli* (Russell's Viper) [1].

Venom of the snake is most complex mixture containing enzymatic and non-enzymatic toxins, non-toxic proteins, also metals. This mixture is stored in the poison glands of snakes. Numerous enzymes are present in venom, some of which are haemorrhagins, cytolytic, necrotic toxins, pre-synaptic and post-synaptic neurotoxins, phospholipases, proteases, nucleosidases, phosphodiesterases. Snake Venom also contains non-protein anticonvulsant cardiotoxin [2].

Use of traditional medicines is generally preferred against snakebites rather than anti-venoms. Medicinal herbal constituents have immense global importance and are recognized as local heritage. In Ayurvedic system, different plants and their phytoconstituents are found to possess anti-venom activity. This review focusses on herbal constituents used in snake poisoning and Herbal antagonists as well as the future prospects of herbal therapy.

Limitations of anti-venom therapy

- Mostly anti-venoms are limited in supply and expensive.
- Strict Storage conditions required such as almost all anti-venoms must be preserved as freeze-dried ampoules. Liquid form anti-venoms must be always kept refrigerated.
- Intramuscular administration of anti-venoms is not that much effective.
- Specific anti-venoms are used against poisons from specific snake species; which could create major problem as, for the treatment of patient; species of the snake that bit him must be known.
- Some Liquid Anti-venoms possess protein precipitation property which can cause decrease in activity thus resulting in susceptibility for adverse reactions.

- Skin Sensitivity testing done for the anti-venoms is itself considered dangerous since it
- Skin Sensitivity testing done for the anti-venoms is itself considered dangerous since it has the risk of inducing acute reactions and delays the initiation of antivenom administration.

Overview of antidotes consisting of herbs

Many plant species are used as medicines for treating poisoning due to snake bites across various parts of the world. These can be used to resist toxic effects of snake venom in various modes such as drinking of herbal extracts, chewing of barks and leaves of various plants, topical application of the sap of plant on bitten area.

Ex: *Ophiorrhiza mungos*, *Peristrophe bicalyculata*, *Calotropis gigantea*, *Aristolochia indica*, *Crinum jagus* etc.

First investigations on herbal antidotes were started and carried out by Knowles but however he failed to report their efficacies against snake bite [3]. On the the hand, Mhaskar and Caius tested with around 300 plant species and their numerous combinations against venom induced lethality but they ignored the systemic changes that are caused by snake venom [4].

Herbs and herbal plant species preferably used against snake envenomation

Herbal plant species name	Part of plant	Active against snake species
<i>Abrus precatorius</i>	Root	<i>Bungarus caeruleus</i> (Indian Krait)
<i>Ophiorrhiza mungos</i>	Root	<i>Daboia russelii</i> (Russell's Viper)
<i>Renealmia alpinia</i>	Rhizome	<i>Bothrops atrox</i> (Common Lancehead)
<i>Curcuma longa</i>	Rhizome	<i>Naja naja</i> (Indian Cobra)
<i>Crinum jagus</i>	Bulb	<i>Echis ocellatus</i> (West African Carpet Viper)
<i>Brownea rosademonte</i>	Stem Bark	<i>Bothrops asper</i> (Terciopelo)
<i>Strychnos nux vomica</i>	Seeds	<i>Crotalus viridis</i> (Western Rattle snake)
<i>Vitis vinifera L</i>	Seeds	<i>Echis carinatus</i> (Saw-Scaled Viper)
<i>Citrus limon</i>	Ripe fruit	<i>Bothrops asper/Bothrops atrox</i>
<i>Crescentia cujete</i>	Unripe fruit	<i>Echis carinatus</i> (Saw-Scaled Viper)
<i>Galactia glaucescens</i>	Leaves	<i>Crotalus durissus terrificus</i> (South American Rattle Snake)
<i>Tabernaemontana catharinensis</i>	Aqueous Extract of plant	<i>Bothrops jararacussu</i> (Jararacussu)
<i>Andrographis paniculata</i>	Ethanollic Extract of plant	<i>Naja siamensis</i> (Thai Cobra)
<i>Annona senegalensis</i>	Methanolic Extract of Root Bark	<i>Naja nigricollis nigricollis</i> (Black-necked Spitting Cobra)
<i>Mimosa pudica L</i>	Aqueous Extract of Dried Roots	<i>Ophiophagus Hannah</i> (King Cobra)

Herbal Antidotes in Brief

Following is the detailed description about herbs used as antidotes along with the info about the venom from respective snake species, which they counteract and their anti-venom action followed by various herbal formulations used as a substitute to Anti-venoms.

Abrus precatorius

Belonging to family Fabaceae and known as Rosary Pea or Crab's eye; is an ornamental, twining, woody vine that grows upto 10–20 ft. The roots of this plant are used in South Africa and Tanzania to cure tuberculosis, bronchitis, snake poisoning, and asthma. It consists of a severely toxic lectin poison called as Abrin, which is a toxalbumen and is least comparable to ricin found in castor seeds. Abrin has two polypeptide chains (A and B) connected by a disulfide bridge [5]. It also consists of Glycyrrhizin present especially in roots of plant.

It's used in counteracting Krait poison. Kraits are of different species and all have extremely severe venom. Kraits are usually found in India and Sri-Lanka also in some parts of Southeast Asia. Krait venom consists of powerful presynaptic and post synaptic neurotoxins which shows their action at nerve endings near the synaptic clefts of brain. Presynaptic neurotoxin is called as alpha bungarotoxin while post synaptic one is called as beta bungarotoxin. These neurotoxins exhibits muscle paralysis by binding to the 2 binding sites present on the nicotinic acetylcholine receptor (nAChR) [6].

Root extracts of *Abrus precatorius* is vastly used to treat *Bungarus caeruleus* venom however it is also effective in treatment of poisoning from almost all Krait species. Sometimes roots are chewed directly for immediate anti-venom effect. However common method of administration of Rosary peas in case of Krait bite is:- 2–3 g of roots are made into paste and consumed along with cold water or cow's milk (Two times a day for 7 days).

Ophiorrhiza mungos

Belonging to coffee family (Rubiaceae) and commonly known as Indian snake root; this plant is the erect, herbaceous, evergreen perennial plant with stems that usually grows 10 - 50cm tall. The plant is harvested mainly in south west China, India, Sri Lanka and other parts of East Asia. It consists of alkaloids such as Camptothecin and 10-Methoxycamptothecin which have excellent anti-viral and anti-cancer properties and hence these plants are used against Herpes simplex virus and against various cancers like colon, lung, ovarian and cervical cancers [7].

Roots of this plants are used in counteracting Russell Viper's deadly venom. The Russell viper (*Daboia russelii*) leads to 30–40% of all snakebites and the most number of life-threatening bites of any snake in Indian sub-continent and Sri-Lanka. The symptoms of Russell's viper bite include high swelling, coagulation of blood, renal dysfunction and neuromuscular paralysis [8]. Russell's viper venom causes death generally by its high potent coagulation activity. It is due to the presence of RVV-X glycoprotein that specifically activate coagulation factors X and V. RVV-X (Russellysin enzyme) contains six N-linked oligosaccharides, four in the alpha- chain and one in each of the beta- and gamma- chains [9].

The present study aims to verify the neutralizing ability of traditional herb *Ophiorrhiza mungos* root extract against Russell's viper (*Daboia russelii*) venom in the early developing chick embryos since anti-venom for Russell's viper doesn't show proper anti-venom activity. The disc impregnated with the combination of both was placed on the yolk sac membrane preferably over the anterior blood vessel of 6th day chick embryo. Higher concentration of root extract remarkably expressed complete abolition of traces of hemorrhagic lesions instigated by viper venom [10].

Renealmia alpinia

An herbaceous perennial plant belonging to family Zingiberaceae; that is often found in colonies and that can reach maximum height of 1-6 metres. It grows from the rhizome which is around 30 cm thick. The plant is known for its use as a medicine, flavourant in food and a dye source. It's habitual in dense mixed forests of Brazil, Peru, Mexico, Caribbean etc. Decoctions of the plant's rhizomes; or its external baths are used as the means of traditional medicine to counteract snake venom. Ethanolic extract of the rhizomes presented the complete potential of this plant in neutralization of *Bothrops atrox* venom within 48 hours when it was injected into mice. It was exhibited due to the antiphospholipase A2 activity [11].

Mass spectrometry was used for characterization of this snake's venom which identified peptides that matched with a single PIII-SVMP (snake venom metalloproteinase) cDNA named Batrotoxrhagin. This component of venom was responsible for inhibition of collagen-induced platelet-aggregation, and thus exhibited haemorrhage and fibrin lysis [12].

Edema, defibrillation effects of *Bothrops atrox* (Common Lancehead) venom were minimized by the use of rhizomes from *Renealmia alpinia*. It also shows partial protection towards haemorrhage caused by Batrotoxrhagin [13]. The Extract of this herb is generally administered subcutaneously to give immediate effect in order to stop the harsh symptoms of *Bothrops* venom. At 75 mg/kg; extracts of *Renealmia alpinia* reduced the extent of venom-induced pulmonary hemorrhage by 48.0%. *Renealmia alpinia* extracts also showed the inhibition of hemorrhage in heart and kidneys. These figures put worth the new hypothesis of considering *Renealmia alpinia* as a prophylactic agent in snakebite [14].

Curcuma longa

Curcuma longa is a yellow-orange polyphenol. Its dry yellow powder that is oil-soluble. Curcuma is deprived of flavor and aroma. It exhibits strong anti-oxidant and anti-inflammatory medicinal properties. It's also called as Turmeric and is commercially available as a yellow powder obtained from grinding rhizomes belonging to family Zingiberaceae. Its active constituent is Curcumin which is the dimer of Vanellin. Hence it's used as a counteracting agent against Arthritis, Alzheimers Disease, chest pain colic pain and hepatic pain. It's also used as colourant and flavourant in food. It exhibits best antiseptic properties.

The venom of *Naja naja* (Indian cobra) consists of cardiotoxins, haemotoxins, cobratoxins, neurotoxins etc. which shows severe effects thus resulting in immediate deaths. Of this Alpha-Cobratoin is much lethal and it is a nicotinic acetylcholine receptor antagonist (short chain alpha-neurotoxin). The cobratoin binds to ligand-binding subunits in the postsynaptic membrane receptor. Thus, binding of acetylcholine and turning its chemical signal into an electric one is prohibited strongly. This results in death of victim by the respiratory paralysis [15].

Turmeric also widely used as an antivenom agent against toxins of Indian cobra. It consist of Turmerin which is a protein that inhibits enzymatic activity and neutralizes cytotoxicity, edema, and myotoxicity of multitoxic phospholipase A2 of Cobra [16]. It was also concluded that Hexane extracts of *Curcuma longa* i.e ar-turmerone showed inhibition of proliferation and natural killer cell activity of human lymphocytes. Other than this, Beta-Sitosterol (a phytosterol) shows 70% neutralization potential of Cobra

venom and Turmeric rhizome contains 1.804 mg of phytosterols per teaspoon [17].

Crinum Jagus

Commonly called as Crinum (family- Amaryllidaceae) is a tender perennial bulb which is native to tropical Africa. These are Tulip like white flowers that are bloomed in clusters during summer season above the leafless stalks. These flowers has the height of about 2-3 feet from the strap shaped green leaves clumps. Aroma of few flowers is strong while others have little fragrance. Crinum bulbs typically taper into elongated necks. The bulbs contains 4 major alkaloids such as lycorine, hamayne, crinamine and 6-hydroxycrinamine. Out of these only crinamine showed strong antibacterial activity.

West African Carpet Viper (*Echis ocellatus*) contains haemorrhagins in their venom namely Zinc-metalloproteinase which causes extensive bleeding. It also causes extreme necrosis of bitten area. In South Africa, envenomation rate of this snake is greater than 80%. It also contains Serine Protease which acts on hemostatis system of victim.

The *Crinum jagus* bulb extract with methanol is used to counteract venom effects of Carpet Viper. It basically acts by preventing myonecrosis and heamorrhage induced by this snake's venom. The peculiarity of *Crinum Jagus* is that it can also be used to counteract venom of other snake species like *Bitis arientas*, *Naja nigricollis* [18].

Galactia glaucescens

Galactia glaucescens (Benth) is native to Central America from Nicaragua to Panama, and widespread in northern South America from Colombia south to Paraguay. This plant found to have a antivenom effect against *crotalus durissus terrificus* venom (South American rattle snake) [19].

Venom of *crotalus durissus terrificus* consists of neurotoxins (crotoxin and crotamine) that cause progressive paralysis. In some cases *C. d. terrificus* bite can cause impaired vision or complete blindness, ptosis, auditory disorders, paralysis of the peripheral muscles, especially neck, which becomes so limp that can be easily broken, and ultimately life-threatening respiratory paralysis. Neurotoxins like Phospholipase A2 causes damage to the heart and skeletal muscle, causing general pain, aches, and tenderness throughout the body [20].

Ethanolic extract of leaves of *Galactia glaucescens* (GGE) in a concentration of 100 and 500 µg/ml found to prevent the neuromuscular paralysis caused by *Crotalus durissus terrificus* venom.

Tabernaemontana catharinensis

Tabernaemontana catharinensis plant belongs to the family Apocynaceae. It is commonly found in the southern South America. The aqueous extract of this plant is found to be active against the venom of *Bothrops jararacussu* (jararacussu) snake.

Venom of *Bothrops jararacussu* consist of two myotoxins namely bothropstoxin-1 and bothropstoxin-2 which causes phospholipase A2 inhibition and inhibit the myotoxic activity. Aqueous extract of *Tabernaemontana catharinensis* found to possess lethal effect in the partial neutralization of the myotoxic effect of the jararacussu venom.

Andrographis paniculata

Andrographis paniculata is annual herbaceous plant belongs to the family Acanthaceae, and it is native to Sri Lanka and India. It is found to be active against the venom of the Indian cobra (*Naja naja*).

The venom of Indian Cobra contains toxins which are composed of enzymes, neurotoxins, proteins and cardiotoxins. These toxins may lead to respiratory paralysis in the victim, which is the major cause of death ^[21]. ASV (Anti-Snake Venom) and ethanolic extracts of the *Andrographis paniculata* can save life in many cases.

Ethanolic extract of *Andrographis paniculata* increases the survival time and protection fold of the victim bitten by the Indian cobra but could not protect from death. It is found more effective when given in the larger amount i.e 2g/kg ^[22].

Annona senegalensis

It is commonly known as wild custard apple, African custard apple belonging to the family *Annonaceae*. The word *senegalensis* mean “of Senegal”, a country from where the specimen is collected ^[23]. The methanolic extract of this plant was found to be active against the venom of black necked spitting cobra (*Naja nigricollis nigricollis*).

The venom of *Naja nigricollis* primarily consist of cytotoxins along with some other components. With highly potent cytotoxins such as necrotic agents it possesses Elapid Neurotoxic properties. Snake bite causes severe external haemorrhaging and tissue necrosis ^[24].

The methanol extract of the root or stem bark of the plant *Annona senegalensis* causes the reduction in the Myonecrosis, Haemorrhage and Hyperthermia caused by the bite of the *Naja nigricollis nigricollis* ^[25].

Mimosa pudica

Also called as sleepy plant, shy plant, Sensitive plant, Action plant, touch me not, Shame plant is a flowering plant belonging to the family *Magnoliopsida & Fabaceae*. The species is Thailand, japan, srilanka, Bangladesh, Indonesia etc. ^[26].

The venom of *Ophiophagus Hannah* (king cobra) primarily contains Neurotoxins. Toxins of king cobra affects the central nervous system of the victim, which results in blurred vision, severe pain, drowsiness and eventually paralysis. In some serious cases cardiovascular collapse is progressed, which causes the victim to fall into coma ^[27]. The aqueous extract of dried roots of *Mimosa pudica* was found to be active against the king cobra's venom.

Conclusion

According to the estimation by WHO, it's been found that about more than 70% of people rely on herbal medicines. But however the use of these medicines against snake's venom is limited and mostly unknown. The analysis and studying of the herbal anti-venoms i.e. Traditional Herbs has been proving to be fruitful and within years of further research it would be possible to avail these formulations against snake bites instead of waiting or depending on anti-venoms which possesses numerous side effects and related problems. There are many factors to study for careful understanding of these natural herbs. From this article few of the factors and usefulness of these herbs can be known.

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