SNAKE BITE, SNAKE VENOM, ANTI-VENOM AND HERBAL ANTIDOTE – A REVIEW
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ABSTRACT
The mortality associated with snake bites is a serious public health problem as the estimated death incidence per year is about 1,25,000 globally. In India about 35,000 to 50,000 people reportedly die of snake bite; although, unreported cases may be even more in rural areas. Considering the socio-medical problem due to snake bite, a review is being conducted on snake bite (management aspects), snake venom (nature and its utility), anti-venom and herbal antidote to provide adequate information to researchers for better future prospective.

KEYWORDS: Snake bite, snake venom, anti-venom, herbal antidote.

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INTRODUCTION
The morbidity and mortality associated with snakebites is a serious public health problem in many regions of the world, particularly in rural areas lacking medical facilities. About 35,000 to 50,000 people reportedly die of snake bite (52 poisonous species of snakes are available in India, majority of bites and mortality are due to Ophiophagus hannah – king cobra, Naja naja – spectacled cobra, Daboia russelli – Russell’s viper, Bangarus caeruleus – common krait and Echis carinatus – saw-scaled viper – Bawaskar1) in India every year specially in rural areas; however, the unreported cases may be even more. Proper first aid and medical support in form of anti-venom may reduce mortality of snake bite to a greater extent. Apart from possessing side effects, anti-venom development is time consuming, expensive and requires ideal storage condition2, and therefore search for venom inhibitors, either synthetic or natural, that could complement or substitute for the action of anti-venoms are of prime importance. Herbal antidotes may be an alternative but information on this aspect is still inadequate. The present article is a review on snake bite, snake venom, anti-venom and herbal antidote which will provide unabridged repository of references as well as knowledge on the aspect to researchers for minimizing socio-medical problem of snake bite in tropical countries, especially in India.

SNAKE BITE
A snake bite is an injury caused by a snake, often resulting in puncture wounds inflicted by the animal’s fangs and sometimes resulting in envenomation. Although majority of snake species are non-venomous and typically kill their prey with constriction rather than venom, venomous snakes (15% out of 3000 known species)3,4,5 are reported to be found on every continent excepting Antarctica3.

Frequency of snake bite
About 35,000 to 50,000 people reportedly die of snake bite in India every year; however, the unreported cases may be more in rural India. Estimated snake bites and (death) cases were reported6 as – 25,000(30) in Europe; 20,000(100) in Middle East; 45,000(15) in USA and Canada; 3,00,000(5,000) in Central and South America; 10,00,000(20,000) in Africa; 40,00,000(1,000) in Asia; 10,000(200) in Oceania - all total world wide 5 million (1,25,000). Death incidence due to snake bite is rather rare in Australia, Europe and N. America but frequent in S. Asia, S.E. Asia and Sub-Saharan Africa3,6,7. In Zimbabwe on 274 cases studied, 4 out of 5 children died who are under 8 years old8.

Poisonous snakes generally possess the characters like - 1. Vertically elliptical shaped cat like pupil. 2. A small depression (termed pit) between the eyes and nostrils. 3.
Triangle shaped head e.g. Copperheads and rattle snakes, exception- Elapids. 4. Underside scales of tail go completely all the way across in a single row from the anal plate; the very tip of the tail may possess two scale rows. 5. Head and body both are seen during swimming time. 6. Generally of multiple colors. 7. Emitting a warning rattle (a dry, whirring sound) e.g. Rattlesnakes, not to be confused by the sound due to the vibration of several other poisonous and non-poisonous snakes.

In contrast, non-poisonous snakes generally possess the characters like – 1.Round pupil in the centre of eye. 2. ‘U’ shaped head. 3. Two rows of scales from the vent to the tail end. 4. Only head is seen during swimming time. 5. Generally of one colour. 6. Mostly stripes are from head to tail.

**Envenomation**

Envenomation is completely voluntary, i.e., all venomous snakes are capable of biting (dry bite) without injecting venom into their victim; practically approximately 20% of snake bites are dry bites. The amount of venom injected varies markedly between species - Gaboon viper deliver 450-600mg venom per bite, the most of any snake.

**General symptoms of snake bite**

The outcome of snake bites depends on numerous factors, including the species and size of snake, the area of the body bitten, the amount of venom injected, and the age and health conditions of the victim. Children are more likely to show severe symptoms because they receive a large concentration of venom due to their smaller body size. Feelings of terror and panic are common after snake bite and may produce a characteristic set of symptoms mediated by the autonomic nervous system. There is vast variation in symptoms between bites from different types of snakes. Most snake bites, whether by a venomous snake or not, will produce some type of local effect. There is minor pain and redness in over 90% of cases, although this varies depending on the site. Bites by vipers and some cobras may be extremely painful, with the local tissue sometimes becoming tender and severely swollen within 5 minutes. This area may also bleed and blister and can eventually lead to tissue necrosis. Other common initial symptoms of pit viper and viper bites include lethargy, bleeding, weakness, nausea, and vomiting. Symptoms may become more life-threatening over time, developing into hypotension, tachypnea, severe tachycardia, severe internal bleeding, altered sensorium, kidney failure and respiratory failure.

Bites caused by the Mojave rattlesnake, kraits, coral snake, and the speckled rattlesnake reportedly cause little or no pain despite causing serious injuries. Victims may also describe a "rubbery," "minty," or "metallic" taste if bitten by certain species of rattlesnake. Spitting cobras and kraits can inject venom in victims' eyes, which results in immediate pain, ophthalmoparesis, and sometimes blindness. Some Australian elapids and most viper envenomations will cause coagulopathy, sometimes so severe that a person may bleed spontaneously from the mouth, nose, and even old, seemingly-healed wounds. Internal organs may bleed, including the brain and intestines and may cause ecchymosis (bruising) of the victim's skin.

Venom emitted from elapids, including sea snakes, kraits, cobras, king cobra, mambas, and many Australian species contain toxins which attack the nervous system, causing neurotoxicity. The victim may present with strange disturbances to their vision, including blurriness. Paresthesia throughout the body, as well as difficulty in speaking and breathing. If the victims are not treated immediately they may die from respiratory failure. Venom emitted from some types of cobras, almost all vipers, some Australian elapids and some sea snakes causes necrosis of muscle tissue. Muscle tissue will begin to die throughout the body, a condition known as rhabdomyolysis which can result in damage to the kidneys as a result of myoglobin accumulation in the renal tubules, resulting in hypotension and acute renal failure, eventually leading to death.

Dry snakebites, and those inflicted by a non-venomous species, can still cause severe injury to the victim by inflicting deep puncture wounds, microbial contaminations, including *Clostridium tetani* harboring in snake's saliva and fangs.

**SNAKE VENOM**

Snake venom (yellow, green or even colorless) is a egg like viscous liquid mainly consisting of toxic protein namely, neurotoxins, cardiotoxins, blood clotting toxins, bleeding toxins and enzymes (>50) and other major components as well as small peptides, amino acids, carbohydrates, lipids, nucleosides, biological amines and metal ions; produced in modified parotid glands normally responsible for secreting saliva, stored in structures called alveoli behind the animal's eyes and ejected through its hollow tubular fangs. Fresh snake venom is neutral or weak acid, and it is alkaline when it is placed for a long time and upon exposure to air fresh venom produces foam and will be non-venomous and putrid when kept at room temperature for 24 hours (toxicity disappear following UV irradiation and heat treatment; dealt with formaldehyde the toxicity also disappear but antigenic property is retained).
Snake venom types
Snake venom is divided into hemolytic and neuropathic types. The hemolytic venom is more effective than the neuropathic type. Based on toxins, the snake venom is classified as blood circulation toxins (e.g. Viper, Trimersurus stejnegeri, Agkistrodon acutus; symptoms: rapid swelling, bleeding, pain, bite region turns purplish, black and necrotic, may cause death due to heart failure if not treated effectively within 4 hours), nervotoxin (e.g. Bungarus fasciatus, B. multicinctus; symptoms: bleeding, swelling, slight fever, anxiety, groaning with pain, difficulties in swallowing and breathing, convulsions, respiratory muscle paralysis and finally death) and mixed toxin (e.g. Cobra and King Cobra; nervous symptoms). Snake toxins possess a great variety in their functions. The two major families are neurotoxin (Fasciculins: attack cholinergic neurons by destroying acetylcholinesterase causing tetany leading to death; Dendrotoxin: inhibits neurotransmission by blocking the exchange of + and – ions across the neuronal membrane, paralyses the nerve, e.g.- Mambas; α-neurotoxin: block Ach flow, feeling of numbness, e.g.- Kraits) and cytotoxin (Phospholipases: enzyme that convert phospholipids molecule to a lysophospholipid- causes hole in cell membrane, e.g.-Japanese Habu snakes; Cardiotoxin: muscle venom and prevents muscle contraction, stops heart beat, e.g.- King Cobra and some other Cobras; Haemotoxin: destroy RBC, slowly progressing venom, e.g.- Vipers and members of Naja genus). Fry reported that snake toxins arisen from recruitment events of genes from within the protein families: acetylcholinesterase, disintegrin/metalloproteinase, AVIT, complement C3, crotasin/beta defensin, cystatin, endothelin, factor V, factor X, kallikrein, kunitz-type proteinase inhibitor, LYNX/SLUR, L-amino oxidase, lectin, natriuretic peptide, betanerve growth factor, phospholipase A(2), SPla/Ryanodine, vascular endothelial growth factor, and whey acidic protein/secretory leukoproteinase inhibitor. Toxin recruitment events were found to occur 24 times in the evolution of snake venom. Calvete et. al. assessed the protein composition of the venom of the East African Gaboon viper (Bitis gabonica gabonica) following RP-HPLC, N-terminal sequencing, MALDI-TOF peptide mass fingerprinting, and CID-MS/MS and found a total of 35 proteins of molecular masses in the range of 7-160 kDa belonging to 12 toxin families. The most abundant proteins were serine proteinases (26.4%), Zn2+-metalloproteinases (22.9%), C-type lectin-like proteins (14.3%), PLA2s (11.4%), and bitiscystatin (9.8%); while, other protein classes bradykinin-potentiating peptides, dimeric disintegrins, Kunitz-type inhibitor, DC-

Utility of snake venom
Snake venoms are used to control heart diseases, high blood pressure, cancer (contortrostatin produced by Agkistrodon contortrix - is cytostatic in nature and found to lower the growth rate of breast cancer in mice), tumor, polio, neurological disorders (enzymes from cobra venom were found to cure Parkinson’s and Alzheimer’s diseases), excessive bleeding (a blood clotting protein in Taipan venom stop bleeding during surgery or after major trauma), blood clotting (ancrod- obtained from Malyan pit viper, used to develop angiotsin converting enzyme inhibitors to treat stroke victims), severe allergies amongst others. Other interesting areas of snake venom include the treatment of viruses (as venom contain phospholipidases which break down cell membrane), aging and some are even used in commercial wrinkle cream!

Snake bite management
There are two important aspects of snake bite management- 1) Proper first aid; 2) Anti-venom serum therapy. Since rural people are forced(lack of proper treatments) to rush to nearby towns and cities to get medical support, precious time is lost in traveling and in organizing transport (scenario may be same universally). Proper first-aid using herbal formula can effectively reduce the fatalities due to snake bites.

ANTI-VENOM
Anti-venom (specific treatment of envenomation is done by parenteral administration of horse or sheep derived polyclonal anti-venom) first developed (anti-ophidic serum) by Calmette (1895) aimed to neutralize venom toxins and was experimented against Indian Cobra (Naja naja).

Anti-venom types
Anti-venoms can be classified into monovalent (when they are effective against a given species' venom) or polyvalent (when they are effective against a range of species, or several different species at the same time) types.

Generic name
Equine (horse derived)/ Ovine (sheep derived) immunoglobuline F(ab’)2 fragments.

Pharmacotherapeutic class
Immunosera and immunoglobulins. ATC code : J06AA3

Equine immunoglobuline F(ab’)2 anti-venoms:
FAV AFRICA polyvalent equine F(ab’)2 anti-venom for Subsahara African snakes : Bitis, Echis, Naja, Dendroaspis.
FAVIREPT polyvalent equine F(ab’)2 anti-venom for Middle East snakes: Bitis, Echis, Naja, Cerastes, Macroviopa.

VIPERFAV polyvalent equine F(ab’)2 anti-venom for European snakes: Vipera

Anti-venom producing centers
Australia CSL, Brasil Instituto Burtantan, Costa Rica Instituto Clodomiro, Croatia Inst. of Immunology, France Aventis Pasteur, France Pasteur Merieux, Germany T wyford, Indonesia Bio Farma, Israel Felsenstein Medical Research, Italy S clave, Mexico M yn Laboratories, Poland Biomed, South Africa SAIMR, Switzerland Schweizerisches Serum- und Impfstitut, Switzerland Institut Sérotherapie et Vaccinal Suisse, Taiwan Nat.Inst.Prev.Med, Thailand Thai Red Cross, USA MSD, USA Wyeth, USA Protherics, South Africa Vaccine Producers PTY Ltd.-Sandringham, China Shanghai Institute of biological products, Ministry of Public Health-Shanghai, Indonesia Biofarma-Bandung, Iran RAZI Vaccine & Serum Research Institute-Teheran, Myanmar Pharmaceutical Factory-Yangon, Pakistan National Institute of Health-Islamabad, Philippines Biologic Production Service, Thailand National Blood Center- Bangkok, Thailand Red Cross Society- Bangkok, Uzbekistan Uzo Bio Pharm-Tasulohken.

Indian centers

Anti-venom selection
Selection of the appropriate anti-venom is a very crucial step. Venom detection kits (available only in Australia – consist of a rapid two stepped enzyme immunoassay in which wells are coated with antibodies to the various snake venoms through a swab from the bite site, blood or urine) help to select the type of anti-venom. When venom type detection is not possible polyvalent anti-venoms are used.

Limitations of anti-venom
1. Cause various side effects. 2. Can’t undo damage already caused by venom, so anti-venom treatment should be started as soon as possible. 3. Mostly administered intravenously but the route may not be uniformly effective. 4. Production is time consuming and expensive. 5. Limited supply. 6. Liquid anti-venom may loose its activity due to protein precipitation, if not stored properly. 7. Must be preserved always as freeze-dried ample.

Side effects of anti-venom
Side effects of anti-venom therapy are anaphylactic reaction (difficulty in breathing and swallowing; hives; itching, especially of feet or hands; reddening of skin, especially around ears; swelling of eyes, face, or inside of nose; unusual tiredness or weakness, sudden and severe), serum sickness (enlargement of the lymph glands; fever; generalized rash and itching; inflammation of joints), pyrogen reaction – probably due to the action of high concentrations of non-immunoglobulin proteins present in commercially available hyper-immune anti-venom.

HERBAL ANTIDOTE
Different plant species (ethanolic/methanolic/aqueous extracts of plant parts) belonging to diverse plant resources (mostly used as folk medicine) is being found to neutralize effectively snake venom. Vitis vinifera L. (family: Vitaceae; part used: methanolic extract of seeds; effective against: Indian Daboia/Vipera russelli, Echis carinatus, Anacardium occidentale L. (Anacardiaceae; methanolic extract of bark; V. russelli, Tamarindus indica L. (Leguminosae; seed extract; V. russelli), Hemidesmus indicus R.Br.(Apo cnaceae; methanolic extract of root; V. russelli, Acalypha indica L. (Euphorbiaceae; ethanolic leaf extract; V. russelli), Andrographis paniculata (Bur.m.f) Ness and Aristolochia indica L. (Acanthaceae/Aristolochiaceae; methanolic plant extract; V. russelli, E. carinatus, Pluche indica L. (Asteraceae; root extract; viper venom, Mucuna pruriens L. (Fabaceae; aqueous seed extract; cobra, Naja sp., Calloselasma rhodostoma, Bangarus caeruleus, Mimosa pudica L. (Mimosaceae; aqueous extract of dried root; N. naja, B. caeruleus, N. naja kaouthia, Ophiopagus hannah, Bungarus candidus, B. fasciatus, C. rhodostoma), Aszadricha indica A.Juss (Meliaceae; methanolic leaf extract; cobra and Russell’s viper), Clerodendrum viscosum Vent. (Verbenaceae; alcoholic root extract; N. naja, Emblica officinalis L. (Euphorbiaceae; root extract; cobra and viper), Curcuma zedoaria Rosc. (Zingiberaceae; aqueous extract; N. naja siamensis), Parkia biglobosa (Jacq.) Bent h. (Mimosaceae; stem bark extract; Naja nigricollis, Echis ocellatus, Boswellia dalzielli Hutch. (Burseraceae; methanolic extract; E. carinatus, Balanites aegyptiaca L. Delile (Balanitaceae; acetone and methanolic extract of stem bark; E. carinatus), Mangifera indica L. cv.’Fahilum’ (Anacardiaceae; ethanolic extract of seed kernel; Thai cobra, Malayan pit viper, C. rhodostoma, N. naja, Echipta prostrata L. (Asteraceae; butanolic extract; Malayan pit viper, Gloydius brevicaudus, G. shedaoensis, G. shedaoensis

ussuriensis\textsuperscript{44}, Deinagkistrodon acutus\textsuperscript{44}, Mouriri pusa Gardn., Byronsonia crassa Niedenzu, Davilla elliptica Hill and Strychnos pseudoquinoa St. Hill.(Melastomataceae, Malpighiaceae, Dilleniaceae, Loganiaceae, respectively; plant extract; Bothrops jararaca\textsuperscript{45}), Croton urucurana Baillon (Euphorbiaceae; aqueous extract; B. jararaca\textsuperscript{46}), Hypericum brasiliense Choyisi (Guttiferae; plant extract; B. jararaca\textsuperscript{47}), Brownea rosadomente C.C.Berg, Tabebuia rosea Bertol. DC., Renealmia alpina (Rottb) Mass, Heliconia curtispatha Pur., Pteleopsis percussa (Cav.) Hook. and Grev., Trichomanes elegans L.C.Rich, Citrus limon (L.) Burm.f., Costus lasius Loes., Sida acuta Burm.f., Dracoutum croatii G.H.Zhu, Bixa orellana L., Struthanthus orbicularis (Kunth) Blume (Caesalpiniaceae, Bignoniaceae, Zingiberaceae, Heliconiaceae, Polypodiaceae, Hymenophyllaceae, Rutaceae, Costaceae, Malvaceae, Araceae, Bixaceae, Loranthaceae respectively; ethanolic extract of stem bark/rhizomes/ whole plant/ripe fruits/ethanolic extract of leaves, branches and stem; Bothrops atrox\textsuperscript{48}), Brongniartia podalryioides H.B.and K., B.intermedia moric. (Leguminosae; root extract; B. atrox\textsuperscript{49}), Casearia sylvestris SW (Flacourtiaceae; aqueous extract; Bothrops genus\textsuperscript{50,51}), Echinacea purpurea (L.)Moench. (Asteraceae; aqueous extract; Bothrops asper\textsuperscript{52}), Cordia verbenacea DC (Boraginaceae; rosmarinic acid from methanolic extract; B. jararacussu\textsuperscript{53}), Baccharis trimera (Less) DC (Asteraceae; metalloprotease snake venom inhibitor; B. neuwied\textsuperscript{54}, B. jararacussu\textsuperscript{54}), Dipteryx alata Vog. (Fabaceae; bark extract; B. jararacussu\textsuperscript{55}, Crotaulus durissus terrificus\textsuperscript{55}, Schizolobium parahyba (Huber ex Ducke) Barney (Caesalpiniaceae; aqueous extract; B. pauloensis\textsuperscript{56}, C. durissus terrificus\textsuperscript{56}), Mikania glomerata Spreng (Asteraceae; aqueous extract; C. durissus\textsuperscript{57}), Musa paradisiaca L. (Musaceae; juice; crotilidae venom\textsuperscript{58}), Crinum jugas L. (Amaryllidaceae; methanolic extract of bulb; Echis ocellatus\textsuperscript{59}, Bitis arietans\textsuperscript{59}, Naja nigricollis\textsuperscript{59}), Argusia argentea (L.f.)Heine (Boraginaceae; methanolic extract; Trimeresurus flavoviridis\textsuperscript{60}, Artemisia campestris L. (Asteraceae; dichloromethane extract of leaf; Macrovoepa lebetina\textsuperscript{61}), Sideritis mugronensis Borja (Lamiaceae; Hypolaetin-8-glucoside, a novel flavonoid; anti-venom activity\textsuperscript{62}) amongst other plant species were found to possess different herbal compounds (acids, alkaloids, steroids, enzymes, peptides, pigments, glycoproteins and glycosides, phenols, pterocarpanes, tannins, terpenoids, quinonoid xanthene and other compounds) which are effective against snake envenomation\textsuperscript{63} by neutralizing different enzymes and toxins (procoagulent enzymes, haemorrhagins, cytolytic or necrotic toxins, phospholipases A2,B,C,D, hydrolases, phosphatases, proteases, esterases, acetylcholine esterase, transaminase, hyaluronidase, phosphodiesterase, nucleotidase, ATPase and nucleosidases) in venoms.

Anti-venom properties are also reported from Ampelozizyphus amazonicus Ducke (Rhamnaceae; stem bark extract\textsuperscript{64}); Humirianthera ampla Miers (Icacinaceae; root extract\textsuperscript{65}); Schumannophyton magnificum (K Schum.) Harms (Rubiaeae; bark extract\textsuperscript{66}); Apuleia leiocarpa (Vog.) J.F.Macbr. (Leguminosae), Brunfelsia uniflora (Pohl) D.Don (Solanaeae), Chiococca brachiata Ruiz and Pav. (Rubiaeae), Cynara scolymus L. (Asteraceae), Dorstenia brasiliensis Lam. (Moraceae), Elephantopus scaber L. (Asteraceae), Marsypianthes chamaedrys (Vahl) Kuntze. (Lamiaceae) and Trianosperma tayuya (Vell.) Mart. (Cucurbitaceae) (plant extract\textsuperscript{67}); Aegle marmelos (L.) Correa (Rutaceae), Centipeda minima (L.) A.Br.and Aschers (Compositae), Aloe vera (L.) Burm.f. (Liliaceae), Phyllanthus niruri L. (Euphorbiaceae), Alstonia scholaris (L.)R.Br.(Apocynaceae), Phyllanthus emblica L. (Euphorbiaceae) (plant extract\textsuperscript{68}); Symlocos sp. (Symlocaceae\textsuperscript{69}); Gloriosa superba L.(Liliaceae\textsuperscript{70}), Achyranthes aspera L. (Amaranthaceae - whole plant extract\textsuperscript{71}), Nerium odorum Soland (Apocynaceae\textsuperscript{72}), Cassia occidentalis L.(Leguminosae – root extract\textsuperscript{71}), Anagalis arvensis L. (Primulaceae\textsuperscript{71}); Jatropha curcas L. (Euphorbiaceae; root extract\textsuperscript{72}); Aristolochia shimadai Hay. (Aristolochiaceae\textsuperscript{73}), Diospyros kaki Thunb. (Ebanaceae\textsuperscript{73}); Leucas aspera (Willd.) Link (Lamiaceae\textsuperscript{74}); Careya arborea Roxb. (Lecythidaceae; bark extract\textsuperscript{75}); Pittosporum neelgherrense Wight and Arnott (Pittosporaceae\textsuperscript{76}); Areca catechu L. (Arecales\textsuperscript{77}) as well.

CONCLUSION
The veracity of the herbal assertions holds a good promise for the development of novel anti-snake venom drug in future. The combination of herbal compounds with anti-venom serum may also be a good prospective as well as effective in neutralizing snake venom. Most importantly herba(s) possessing anti-venom serum activity should be properly identified (plant parts/compound) and cultivated, and knowledge must be disseminated properly so that at least first aid treatments can be provided to reduce mortality of snake bite. Till date proper herbal formulations and its efficacy in relation to remedial measure against snake bites are yet not known properly, and research should be triggered in this direction.

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