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Ethnomedicinal plants and isolated compounds against Snake venom activity: A review

Bhavya J[1], Vineetha M S[1], Veena S. More[2], Farhan Zameer[1], Uday Muddapur[3], Sunil S. More[1]* and Govindappa M[4]

[1]School of Basic and Applied Sciences, Dayananda Sagar University, Bangalore 560111, Karnataka, India

[2]Department of Biotechnology, Sapthagiri College of Engineering, Bangalore 560057, Karnataka, India

[3]Department of Biotechnology, K.L.E Technological University, Vidyanagar, Hubli 580030, Karnataka, India

[4]Department of Botany, Davangere University, Tolahunase Davanagere 577002, Karnataka, India

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Snakebite is an occupational hazard that has affected the population in tropical and subtropical countries. Worldwide approximately 5.4 million bites, 2.7 million envenomations, and 81,000-1,38,000 deaths are observed per annum. The incidences are higher among farmers and plantation workers. Antivenom is the only treatment available and the production of the same is challenging due to geographical variation of snakes, storage conditions, and non-availability of venom for production. Antivenom therapy is associated with immediate or delayed hypersensitivity and does not prevent local tissue damage. Thus the search for medicinal plants by the scientific community has become relevant. The ethnobotanical studies on various plants have revealed their use to treat various ailments including snakebite. Hence, the review is aimed to amass the medicinal plants studied and also emphasize various components isolated that have shown promising results.

Keywords: Antivenom, *In-vitro*, *In-vivo*, Plant bioactive compounds, Snakebite.

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Introduction

Snakebite, an occupational and environmental hazard is a common occurrence in tropical and subtropical countries[1]. It is common in agricultural countries affecting farmers and plantation workers leading to a significant increase in mortality and morbidity. In 2009, World Health Organization (WHO) has declared snakebites as a neglected tropical disease[1,2]. The precise number of deaths due to snakebite is not properly established and it continues to be a public health problem in most countries.

Approximately, 5.4 million snake bites occur globally with 2.7 million envenomation and around 81000 - 1,38,000 deaths annually[3]. In 2008, Kasturiratne and colleagues[4] reported 4,21,000 - 18,41,000 envenomings and 20,000-94,000 deaths. South and Southeast Asia, sub-Saharan Africa, Central and South America were found to have a high number of incidences; India reported the highest number of bites (81,000) and deaths (11,000) in a country[4].

The most effective antagonist of snake venom is the anti-snake venom (ASV). It is the F(ab) fragments of IgG purified from the serum or plasma of a horse, donkey, or sheep that has been immunized with the venom of one or more species of snakes. The serum antivenom invented by Albert Calmette's in 1895 was put to practice for treating envenomations with proper clinical trials. It neutralizes the toxicity of a particular species (monovalent/monospecific) or different species (polyvalent/polyspecific). The antibodies raised against the venom of a particular species may also neutralize the venom of a closely related species (para specific activity)[2].

The principal drawback of serum therapy is its specificity. The variation in species were found; there is a Russell's viper, four cobras and eight species of krait; two subspecies of saw-scaled viper. Moreover, Russell viper also exhibits regional variation. Hence, the composition variability and antigenic reactivity of the venom restricts the use of ASV[5,6].

The non-availability of venom has led to the decrease of antivenom production, the Wildlife Protection Act has indicated that snakes cannot be collected or venom cannot be extracted without permission from wildlife authorities. Therefore the authorities object to capturing snakes in large numbers[5]. Also, the side effects, storage, and logistic

*Correspondent author
Email: sunilacr@yahoo.co.in

problems have made the scientific community look for alternative medicine.

Plants and their parts have been used to treat various ailments for centuries due to their medicinal value. Traditional healing plays an important role in many parts of the world for maintaining the physical and psychological well being of the people. Traditional medicine run in families for years and is handed down by elders to their progeny. In this regard, India has been considered as one of the 12 mega diversity countries in the world. The Eastern Himalayas and the Western Ghats are two out of the 25 hotspots in the world. There are 550 ethnic tribes in India with traditional and indigenous knowledge about the plants[7].

The Sugali tribes of Yerramalais of Kurnool district have been found to use 23 medicinal plants to treat snake bites. They have used individual plant parts or decoction of the plants to treat bites of the cobra, *Bungarus caeruleus*, and *Bungarus fasciatus*[8]. *Allium cepa* and *Tagetes minuta* plants are used extensively to treat snake bites by the Kamba tribes of Kenya. These are used in the form of infusions, decoction or macerations[9]. Bhandary *et al.*[10] reported that Siddis of Uttara Kannada district have claimed smoking of beedis using dried leaves of *Holarrhena antidyscentrica* would render a person insensitive to snake venom. Rani *et al.* has reported that *Kanikkar* tribals of Agasthiarmalai Biosphere Reserves, Western Ghats, Tamil Nadu (India) use 174 ethnomedicinal plants for treating various ailments out of which, fresh leaves or roots with seeds of *Abrus precatorius* L and root paste of *Polygala javana* DC are used to treat any kind of poisonous bites[11]. Alagesaboopathi has reported that the Kurumba tribals of Dharmapuri district use *Ailanthus excels* Roxb., *Andrographis paniculata* Nees, *Cleome viscose* L, *Pergularia daemia* plant parts to treat snake bites[7].

In Kerala, the indigenous group 'Kani' has been treating snake bites using 'Vishakallu' (poison stone). The stone would be placed directly on the bitten area, it absorbs the poison by sticking to the body and detaches itself when the absorption seems to be complete[12]. The ingredients of Vishakallu stone were leaves of *Ocimum sanctum*, *Anisomeles malabarica*, *Leucas aspera*, *Piper betle*, *Santalum album* and pebbles from the river bank[13]. The aqueous paste and decoction obtained from the leaves of *Andrographis paniculata* were also widely used for snakebite by indigenous people of Southern India[12]. The bitter taste of some leaves and roots were also sometimes used for prognostic purposes[14-16]. If the plant material tastes bitter, the patient was judged free from danger, but if the materials remain sweet to taste, the patient needs urgent medical attention. Dosages were repeated until the taste returns to normal. Sometimes, especially when a patient cannot open his/her mouth, the juice of the plant would be administered through nostrils or eyes or applied liberally to the head[17,18]. A strict and complete dietary schedule for swelling, nausea, pain and other effects during and after recovery is followed to promote a thorough cure[14]. People in some areas believe that brushing the teeth daily with the stick of *Tephrosia purpurea*[19] and *Azadirachta indica*[20] would make the body resistant against the snake venom. The Kani group externally applies oil extracted from the leaves of *Aristolochia tagala*, especially during night times to prevent snakebite[21]. The bark powder of *Moringa oleifera* was believed to have antisnake properties if sprinkled near the house to ward off snakes[22].

Mahishi *et al*.,[23] have reported that *Acalypha indica* L., *Rauvolfia serpentina* Benth. ex Kurza, *Elaeodendron glaucum* Jacq.f., *Tylophora asthmatica* Wight et Arn., *Canthium parviflorum* Lam. and *Calotropis procera* R. Br. are used by the local communities of the Shimoga district to treat snake bites. Prakasha *et al*. has reported that *Rauvolfia serpentina* ex. Kurtz, *Alstonia scholaris* R. BR., *Vitex negundo* L. and *Erythrina indica* Lam are used to treat snake bites as folk medicine in NR Pura taluk of Chikmagalur[24]. Hiremath and Taranath have reported that 15 plants are used by the traditional healers of the Chitradurga district to treat snake bites, some of them are *Todalia asiatica* (L.) Lam, *Azima tetracantha* Lam, *Canthium parviflorum* Lam, *Calotropis gigantea* (L), *Urtica dioica* L., *Tylophora asthmatica* (L.f) Wright & Arn., *Acacia arabica* Benth., *Tinospora cordiafolia* (Willd.) Hook[25]. Shiddamallayya *et al*. has reported that *Albizia lebbeck* (L.) Willd, *Clitoria ternatea* L., *Mimosa pudica* L and *Saraca asoca* (Roxb.) de Wilde are used by local people and Vaidyas to treat snake bites as mentioned in the ethnobotanical survey of medicinal plants[26]. Joshi and Tyagi[27] have reported that many medicinal plants in Uttarkhand were used to treat various ailments. *Achyranthes aspera*, *Aconitum atrox*, *Centella asiatica*, *Delphinium vestitum*, *Ficus religiosa* plants and their parts are used for snakebite treatment[27]. Chopra and Nayar have reported that the *Carissa spinarum* L. had been used to treat snakebite by traditional healers[28]. Some of the traditional plants used for the treatment of snakebite according to ethnobotany and ethnopharmacological survey has been tabulated (Table 1).

Table 1 — Plants used by the traditional healers/ tribal population against snakebite in India

Plant	Family	Parts used
Abrus precatorius	Leguminosae	Roots, leaf[29,12,11,30]
Abutilon indicum	Malvaceae	Leaf, Fruits[12,31]
Acacia arabica Benth	Mimosaceae	Leaf [32,25]
Acacia leucophloea	Mimosaceae	Bark[12,31]
Acalypa indica	Euphorbiaceae	Leaf[23,12,31]
Achillea millefolium	Asteraceae	Whole plant[12,31]
Achyranthes aspera	Amaranthaceae	Leaf, Stem, root [12,32,33,34,8,25]
Acorus calamus	Araceae	Rhizome[12,35,36]
Aegle marmelos	Rutaceae	Root bark[12,37,35]
Aerva lanata	Amaranthaceae	Rhizome[12,31]
Aeschynomene indica L.	Fabaceae	Leaf[38]
Aglaia roxburghiana Hiern	Meliaceae	Leaf [38]
Alangium salvifolium	Alangiaceae	Root bark[12,30,8,39]
Allium cepa	Liliaceae	Skin bulb[12,31,33,39]
Alstonia venenata	Apocyanceae	Stem bark[8,40]
Ammania bacifera	Lythraceae	Whole plant[8]
Amaranthus viridis L.	Amaranthaceae	Stem[8]
Ailanthus excels Roxb	Simaroubaceae	Leaf [31]
Anaphyullum beddomei Engl.	Araceae	Rhizome[41]
Andrographis paniculata	Acanthaceae	Leaf, Whole plant[12,7,30]
Andrographis lineata	Acanthaceae	Leaf, flower[12,42]
Argemone mexicana	Papaveraceae	Leaf, root[12,43]
Aristolochia indica	Aristolochiaceae	Root[12,25,41,44,45]
Azadirachta indica	Meliaceae	Flower, leaf[12,31,33,34]
Azima tetracantha Lam.	Salvadoraceae	Leaf [25,37]
Biophytum candolleanum Wight	Oxalidaceae	Leaf [38]
Blepharispermum petiolare DC	Asteraceae	Leaf and stem bark[38]
Balanites aegytiaca (L.) Del	Balanitaceae	Fruit[39]
Barleria prionitis	Acanthaceae	Root[8]
Bacopa monnieri (L.)	Scrophulariaceae	Whole plant[34]
Boerhaavia diffusa	Nyctaginaceae	Whole Plant[46,34]
Butea monosperma (Lam). Taub.	Fabaceae	Bark[24,33]
Butea superba	Fabaceae	Flower[30]
Caesalpinia bonduc	Caesalpiniaceae	Seeds[12,31]
Calendula officinalis	Asteraceae	Flower[12,31]
Calotropis gigantea	Asclepiadaceae	Root, latex[12,25,32,44]
Calotropis procera	Asclepiadaceae	Root, latex[23,33]
Canarium strictum Roxb	Bursariaceae	Resins[47]
Canthium parviflorum Lam.	Rubiaceae	Root[23,25]
Cassia alata	Caesalpiniaceae	Leaf[12,31,37]
Cassia occidentalis	Caesalpiniaceae	Leaf [33,48]
Cassia tora	Caesalpiniaceae	Leaf[12,31]
Cardiospermum halicacabum	Sapindaceae	Leaf [30]
Ceiba pentandra (L.) Gaertn	Malvaceae	Root[8]
Cissampelos pariera	Menispermaceae	Root[31]
Citrulus colocynthis	Cucurbitaceae	Root[33]
Citrus limon	Rutaceae	Ripe seed[12,30,31]
Clitoria ternatea L.	Leguminosae	Root[41,26,34]
Clerodendrum serratum	Verbenaceae	Leaf [34]
Clinacanthus mutans	Acanthaceae	Leaf[12,31]
Cleome viscose L.	Capparidaceae.	Leaf[7]

(*Contd.*)

Table 1 — Plants used by the traditional healers/ tribal population against snakebite in India (*Contd*.)

Plant	Family	Parts used
Commelina benghlensis L	Commenlinaceae	Roots[47]
Cordia dichotoma Forst. f.	Boraginaceae	Whole plant[39]
Corallocarpus epigaeus	Cucurbitaceae	Root[8]
Cipadessa baccifera (Roth) Miq	Meliaceae	Leaf , root bark[30,38]
Curcuma longa	Zingiberaceae	Rhizome[12,31]
Cymbopogon citrates	Poaceae	Whole plant[12,31]
Cyperus rotundus	Cyperaceae	Rhizome[12,31,34]
Cyathea spinulosa Wall ex Hook.	Cyathaceae	Rhizomes[47]
Cyphostermma auriculata (Roxb.)	Vitaceae	Bark[49]
Cyclea peltata (Lam.) Hook. f. & Thoms	Menispermaceae	Root[30]
Dalbergia melanoxylon	Fabaceae	Stem bark[12,31]
Delphinium denudatum Wall. ex Hook. f & Thomson	Ranunculaceae	Root[48]
Eclipta alba	Compositae	Whole plant[12,31,34]
Eclipta prostrata	Compositae	Leaf[12,31]
Ehretia buxifolia	Ehretiaceae	Root[12,31]
Euphorbia hirta	Euphorbiaceae	Whole plant, leaf[12,30,31]
Erythrina indica Lam	Papilionaceae	Leaf[24]
Erythrina excelsa	Fabaceae	Bark[12,31]
Feronica limonia	Rutaceace	Root[12,31]
Gloriosa superba	Liliaceae	Roo tuber[15,30,41]
Gymnea sylvestre	Asclepiadaceae	Root[12,29,30,31]
Glycine max	Leguminosae	Seeds[12,31]
Grewia gamblei Drumm.	Tiliaceae	Leaf and root bark[31]
Habenaria roxburghii (Peers) *R.Br.*	Orchidaceae	Root[31]
Helicteres isora L.	Sterculiaceae	Root[31]
Helianthus ammus	Asteraceae	Seed[12,31]
Heliotropium indicum L.	Boraginaceae	Leaf[30]
Heliotropium ovalifolium Forssk.	Boraginaceae	Sap[50]
Hemidesmus indicus	Asclepiadaceae	Root[12,30,31]
Holarrehena antidyscentrica Roxb	Apocyanceae	Leaf[10]
Holarrhena pubescens (Buch-Ham.)	Apocyanceae	Stem bark[8,30]
Hopea ponga (Dennst.) Mabb.	Diptercarpaceae[26]	
Holoptelea integrifolia (Roxb.) Planch.	Ulmaceae	Stem bark[30]
Isonandra lanceolata Wight	Sapotaceae	Leaf, unripened fruit and root bark[38]
Ixeris sagittarioides (C.B.Clark) Stebb.	Asteraceae	Root[48]
Indigofera tingtoria L.	Leguminosae	Root[41]
Ipomoea pes-tigridis L.	Convolvulaceae	Root[34]
Kalanchoe pinnata (Lam.) Pers.	Crassulaceae	Leaf[30]
Lantana indica Roxb.	Verbenaceae	Leaf[8]
Lantana camara	Verbenaceae	Stem, flower, root[34]
Leucas aspera (Willd) Spreng	Lamiaceae	Leaf , flower[24,31]
Leucas cephalotes	Lamiaceae	Leaf[12,33]
Luffa cylindrical (L.) Roem	Cucurbitaceae	Fruit, Leaf[8,49]
Lindenbergia muraria (Roxb.) Brühl	Scrophulariaceae	Leaf [43]
Lobelia nicotinaefolia Heyne	Compunalaceae	Leaf[24]
Madhuca longifoila L.	Sapotaceae	Nut[12]
Morus alba	Moreaceae	Leaf[12,31]
Moringa pterygosperma	Moringaceae	Gum[25]
Momordica charantia	Cucurbitaceae	Flower[12,30,31]
Momordica balsamina	Cucurbitaceae	Flower[33]
Moringa oleifera	Moringaceae	Bark root[12,31,41]
Musa paradisiacal L.	Musaceae	Stem bark[12,31,41,48]

(*Contd*.)

Table 1 — Plants used by the traditional healers/ tribal population against snakebite in India (*Contd*.)

Plant	Family	Parts used
Murraya paniculata (L.) Jack	Rutaceae	Leaf/ root[8]
Mimosa pudica	Mimosaceae	Leaf[12,26,30]
Nicotiana tabacum	Solanaceae	Leaves[12,31]
Nerium oleander	Apocyanceae	Seeds[12,31]
Ocimum basilicum	Lamiaceae	Whole plant[12,31]
Ocimum sanctum	Lamiaceae	Leaf[12,31,33]
Oldenlandia diffusa	Rubiaceae	Whole plant[12,31]
Oldenlandia umbellate	Rubiaceae	Leaf root[12,31]
Ophiorrhiza mungos	Rubiaceae	Root [12,25,37]
Opuntia dillenii (Ker-Gawl.) Haw.	Cactaceae	Phyllode[30]
Pavetta breviflora	Rubiaceae	Stem bark [50]
Paris polyphylla Smith	Liliaceae	Root[48]
Pedicularis pectinata Wall. ex Benth.	Scrophulariaceae	Leaves, seed, root [48]
Pergularia daemia (Forssk). Chior	Asclepiadaceae	Leaf [7]
Phyllanthus emblica	Euphorbiaceae	Fruit[12,31]
Phyllanthus niruri	Euphorbiaceae	Flower[12,31]
Phyllanthus reticulates	Euphorbiaceae	Leaf[12,31]
Piper nigrum	Piperaceae	Flower[12,24,31]
Pluchea indica	Asteraceae	Seed flower[12,31]
Plumbago zeylanica L.	Plumbaginaceae	Root [30]
Punica granatum	Punicaceae	Whole plant[12,31,37]
Rauvolfia serpentina	Apocynaceae	Root [12,24,30,47]
Rhinacanthus nasutus	Acanthaceae	Leaf [8,40]
Rubia cordifolia		Stem[46]
Sarcostemma intermedium Decaisne	Asclepiadaceae	Stem [50]
Sanseviera roxburghiana Schult. & Schult. *F*.	Agavaceae	Rhizome[30]
Sapindus emarginatus	Sapindaceae	Bark[12,31]
Saraca asoca (Roxb).	Asclepiadaceae	Bark[26]
S. cordifolia L.	Malvaceae	Root, leaf [43]
Semicarpus anacardium	Anacardiaceae	Root[12,31]
Solanum torvum	Solanceae	Flower[12,31]
Sida acuta Burm. f.	Malvaceae	Leaf [34]
Strychnos nux vomica	Loganiaceae	Stem bark leaf; root tuber[8,12,30,50]
Syzygium cumini	Myrtaceae	Stem bark[12,31,37]
Tabermonotana divaricata	Apocynaceae	Root[24]
Teprhosia purpurea	Leguminosae	Root[12,31]
Todalia asiatica (L.) Lam	Rutaceae	Leaf[25,37]
Tiliacora acuminata (Lam.) Miers	Menispermaceae	Leaf[30]
Thymus vulgaris	Lamiaceae	Whole plant[12,31]
Terminalia arjuna	Combretaceae	Bark[12,31,32]
Tinospora cordiafolia	Minispermaceae	Leaf [25,32,37]
Trichodema zeylanicum	Boraginaceae	Root[12,31]
Tragia involucrate	Euphorbiaceae	Whole plant[12,31]
Trianthema portulacastrum L.	Aizoaceae	Root[30]
Tylophora indica	Asclepiadaceae	Leaf, root[8,42]
Tylophora asthmatica (L.f) Wright & Arn.	Asclepiadaceae	Root [23,25,32]
Tylophora longifolia	Asclepiadaceae	Leaf flower[12,31]
Urtica dioica L.	Urticaceae	Root [25,37.49]
Viscum articulatum Burm. f. *var. articulatum* Hook. f	Loranthaceae	Aerial parts [50]
Vitex negundo	Verbenaceae	Leaf[12,24,31,30]
Wattakaka volubilis (L. f.)	Asclepiadaceae	Root, Leaf [50,30,8]
Withania somnifera	Solanaceae	Root [24]
Wedelia calendulae	Asteraceae	Leaf[12,31]
Wrightia arborea (Dennst.) Mabberly	Apocynaceae	Latex[30]

***In-vitro* studies**

The first scientific investigation on herbal antidotes was reported by Knowles in 1921. He screened many plants and their phytoconstituents but failed to report the efficacy against snake envenomation. Later in 1931, Mhaskar and Caius challenged the effectiveness of herbal antidotes by using 314 plants in 180 combinations against Indian snakes[51]. The effectiveness of the herbal antidotes on the systemic effects and lethality induced by the snake venom was questioned and discussed to date. The studies on herbal allies have been carried out by many pioneering scientists to derive extract/phytochemical which would neutralize the effects of venom and also be an alternative to the ASV.

Aristolochic acid from *Aristolochia radix* has been reported to inhibit the enzymatic and pharmacological activities of PLA_2 induced by *Vipera russelii* venom[52,53]. Inhibition of azocaseinolytic activity of *Bothrops jararaca* venom has been observed with the extract of *Masypianthes chamaedrys*[54]. Antihyaluronidase activity of *Mimosa pudica* plant/extract was observed against *Naja naja, Vipera russelii*, and *Echis carinatus* venoms[55]. The butanolic extract and purified butanolic extract of *Eclipta prostrata* aerial parts showed low inhibitory effect on Phospholipase A_2 and did not inhibit the proteolytic activity of Malyan pit viper[56]. Prolongation of clotting time of blood plasma was observed with *Brownea rosa-de-monte*, *Pleopeltis percussa*, *Bixa orellana*, and *Heliconia curtispatha*, *Trichomanes elegans*, after pre-incubation with venom[57]. Neutralization of PLA_2 activity has been documented with seed extract of *Strychnos nux-vomica*[58].

4-nerolidylcatechol has been isolated from the *Piper* species. Various species of the plant are reported to inhibit PLA_2 activity from venoms of Bothrops species[59]. Lupeol acetate from roots of *Hemidesmus indicus* significantly neutralized PLA_2 activity induced by Russell's Viper[60]. Tamarind seed extract inhibited the PLA_2, protease, hyaluronidase, L-amino acid oxidase and 5′-nucleotidase enzyme activities of *Vipera russelli* venom in a dose-dependent manner. The major hydrolytic enzymes are responsible for the early effects of envenomation, such as local tissue damage, inflammation and hypotension. Furthermore, the extract neutralized the degradation of the Bβ chain of human fibrinogen and indirect hemolysis caused by the venom. It was also observed that the extract exerted a moderate effect on the clotting time, prolonging it only to a small extent[61]. *Withania somnifera* has yielded a glycoprotein inhibitor, found to be effective in cobra and viper bite. The compound inhibited the PLA2 activity of *Naja naja*[62].

Inhibition of enzymatic activity has been reported with extracts of *Casearia sylvestris* in experimental animals, injected with lethal doses of Bothropic venoms[63]. Methanolic leaf extract of *Azadirachta indica* has shown significant inhibition of PLA_2 enzymes of Cobra and Russell's Viper venoms[64].

Significant inhibition of PLA_2 activity induced by *Bothrops pauloensis* and *Crotalus durissus terrificcus* venoms is documented with the leaf extract of *Schizolobium parahyba*[65]. Neutralization of *Vipera russelii* venom enzymes, namely phospholipase, protease and hyaluronidase is reported with the bark extract of *Anacardium occidentale* in a dose-dependent manner[66]. Plant extracts of *Andrographis paniculata* and *Aristolochia indica* effectively inhibited the main toxic enzymatic effects of *Echis carinatus*, responsible for a large number of deaths in India. Inhibition of PLA_2 and neutralization of procoagulant activity was observed with both the extracts[67]. Abolition of hyaluronidase and proteolytic activities of viper venom with methanolic extract of *Vitis vinifera* seeds has been reported[68]. *In-vitro* tests with polyphenols from *Areca catechu* L. and *Quercus infectoria Oliv* showed inhibition of PLA2, proteases, hyaluronidase and L-amino acid oxidase of *Naja naja kaouthia* and *Calloselasma rhodostoma* venoms[69].

Different extracts of *Symplocos cochinchinensis* (Lour.) S. Moore ssp. *Laurina* inhibited the *in-vitro* HRBC lysis and lethality induced by *Daboia russelli* venom *in-vivo*[70]. Different extracts of *Acalypha indica* inhibited the *in-vitro* HRBC lysis and lethality induced by *Daboia russelli* venom *in-vivo*[71]. The aqueous extract of *Mangifera indica* stem bark inhibited the enzymatic activities, lethality, oedema, haemorrhage, and myotoxic effect induced by the *Vipera russellii* venom[72]. The *Naja naja* venom induced coagulant, Phospholipase A_2, fibrinolytic activities were effectively inhibited by the aqueous extract of *Emblica officinalis* fruit, leaves of *Ocimum sanctum*, bark of *Azadirachta indica* and bulbs of *Allium sativum*[73]. The *Rauvolfia serpentina aqueous* plant extract neutralized the procoagulant, direct and indirect haemolytic activities induced by *Daboia russelli* venom[74].

Methanolic extract of fresh leaves of *Camellia sinensis* showed inhibition of PLA_2, hyaluronidase, L-amino acid oxidase in venoms of *Naja naja kaouthia* and *Calloselasma rhodostoma*, by *in-vitro* neutralization[75].

***In-vivo* studies**

Prolongation of clotting time of *Echis carinatus* venom treated blood has been observed with the aqueous extracts of *Mucuna pruriens, Strophanthus hispidus*, and *Strophanthus gratus*[76]. The organic acid from the root extract of *Hemidesmus indicus* significantly antagonized hemorrhagic, coagulant and anticoagulant activities in experimental rodents, induced with viper venom[77]. Inhibition of fibrinocoagulation activity induced by *Bothrops jararaca* venom was reported with the extracts of *Masypianthes chamaedrys*[78]. The butanolic extract and purified butanolic extract of *Eclipta prostrata* aerial parts reduced the lethality and hemorrhagic lesion formation induced by *Calloselasma rhodostoma* (Malyan Pit viper)[56].

Plant polyphenols from the aqueous extracts of *Pentace burmanica*, *Pithecellobium dulce*, *Areca catechu* inhibited the lethality of the *Naja kaouthia* venom (4 LD_{50}), the venom necrotizing activity at a minimum dose and also inhibited acetylcholinesterase activity. The aqueous leaf galls extract of *Quercus infectoria* had minimum inhibitory effect on *Naja kaouthia*[79]. The methanolic bulb extract of *Crinum jagus* significantly protected mice from death, myonecrosis and haemorrhage induced by *Echis ocellatus*, *Bitis arietans*, and *Naja* nigricollis venom[80].

The aqueous dried roots of *Mimosa pudica* showed significant inhibitory effects on lethality, phospholipase activity, oedema forming activity, fibrinolytic activity and hemorrhagic activity induced by the *Bungarus caeruleus* venom[81]. Methanolic extracts of *Mouriri pusa Garden, Byrsonima crassa Niedenzu, Davilla elliptica St. Hills* upon evaluation have shown complete neutralization of local haemorrhage. Flavonoids namely myricetin, quercetin, amenthoflavone have been attributed antihemorrhagic potential. Quercetin is a potent lipoxygenase inhibitor[82]. The aqueous extract of leaves of *Schizolobiumparahyba* significantly inhibited the coagulant, hemorrhagic and fibrinogenolytic activities induced by *Bothrops pauloensis* and *Crotalus durissus terrificcus* venom and their isolated toxins[65]. *In-vivo* tests with polyphenols of *Areca catechu* L and *Quercus infectoria Oliv* showed inhibition of the hemorrhagic activity of *Calloselasma rhodostoma Kuhl* venom and dermonecrotic activity of *Naja kauothia* venom[69].

The aqueous extract of *Mucuna pruriens* seeds showed a significant inhibitory effect on the lethality, phospholipase activity, oedema forming activity, fibrinolytic activity and haemorrhagic activity induced by *Bungarus caeruleus* and *Naja naja* venom[83]. The *Serjania erecta* crude extract and fractions neutralized the toxic activities of *Bothrops jararacussu* snake venom and isolated myotoxins (BthTX-I and II). The phospholipase A_2, fibrinogenolytic, myotoxic and hemorrhagic activities were also inhibited by the extract. The myotoxic and edematous activities induced by BthTX-I, and phospholipase A_2 activity induced by BthTX-II, were inhibited by the extract of *S. erecta* and its fraction. The clotting time on bovine plasma was significantly prolonged by the inhibitory action of fractions SF3 and SF4[84].

The ethanolic extract of the *Crescent curette* fruit pulp inhibited the lethality and hemorrhagic activity induced by the *Vipera russelli* venom[85]. The ethanolic extract of *Rauwolfia serpentina* inhibited the phospholipase A_2 and procoagulant activity; inhibited *Naja naja* venom-induced lethality[86]. The aqueous extract of *Rauvolfia serpentina* effectively neutralized the *Vipera russelli* venom lethality and effective dose was found to be 10.99 mg/ 3LD_{50} of venom[74]. The ethanolic root extract of *Piper longum* inhibited the *Vipera russelii* induced haemorrhage in chicken embryos. It also inhibited lethality, haemorrhage, necrosis, defibrinogenation, and inflammatory paw oedema in mice in a dose-dependent manner. It also reduced venom-induced mast cell degranualtion in rats[87].

The ethanolic extract of *Cordia macleodii* bark inhibited the *Naja naja* venom-induced lethality, haemorrhage lesion, necrotizing lesion and oedema in rats. The extract was effective in neutralizing the coagulant and defibrinogenating activity. The cardiotoxic effects in isolated frog heart and neurotoxic activity studies on frog rectus abdominus muscle were also antagonized by the extract[88]. The *Ophiorrhiza mungos* aqueous root extract neutralized the *Vipera russelli* venom-induced lethality and haemorrhage in fertile chick embryos[89]. The *Vitis vinifera* seed neutralized the hemorrhage; partially inhibited procoagulant activity and abolished the

degradation of α-alpha and β-beta chains of human fibrinogen against viper venom-induced effect[90].

Inhibition of haemorrhage and dermonecrotic activities of venoms *in-vivo* was reported with methanolic leaf extracts of *Camellia sinensis*. The action has been attributed to the complexation and chelation of plant phenolic compounds and venom proteins[75].

Eclipta alba was documented to inhibit PLA_2 activity[91]. Neutralization of haemorrhage due to viper venom was documented with seed extract of *Strychnos nux-vomica*[58].

A decrease in oedema formation with aqueous extracts of *Casearia sylvestris* Sw. has been noted in rats injected with lethal doses of Bothropic venoms. Ellagic acid has inhibited edematogenic activity due to total venom and phospholipase A2 (PLA_2) from *Bothrops jararacussu*[63].

Methanolic extract of seeds of *Vitis vinifera* L. has shown promise for the treatment of local effects of viperine bites. The extract neutralized the oedema-inducing property of venom[68]. *Cordia verbenacea* extract significantly reduced paw oedema, induced by *Bothrops jararacussu* snake venom[92]. Table 2 represents the plant extracts or combinations being practised against different snake species and their study.

Table 2 — List of the plants/plant extracts evaluated for their antivenom activity against various species of snakes

Plant	Snake species	Study
314 plants, 180 combinations	*Naja naja* , *Vipera russelli*	Lethality[93]
Aristolochia	*Naja naja* , *Viper russellii*,	
Trimeresurus flavoviridis	Toxic effect, PLA2, Hemorrhage activity[52]	
Curcuma sps	*Naja naja siamensis*	Inactivated postsynaptic neurotoxin of the[94]
Mucuna pruriens, *Strophantus gratu, Strophantus hispidus*	*Echis carinatus*	Prolongation of clotting time[76]
Hemidesmus indicus	*Vipera russelli*	Hemorrhage, coagulant, lethality[77]
Brownea rosademonte, Tabebuia rosea, Heliconia curtispatha, Trichomanes elegans, *Bixa orellena, Phylodendrum tripatitum, Struthanthus orbicularis, Gozalagunia panamensis, citrus limon* and *Ficus nymphaeifolia*	*Bothrops atrox*	Neutralized the haemorrhage[95]
Guiera senegalensis	*Echis carinatus, Naja nigricollis*	Increase in survival time[96]
Mucuna pruriens	*Echis carinatus*	Inhibited the myotoxic, cytotoxic and coagulation activities induced by the venom[97]
Mimosa pudica	*Naja Kaouthia*	Inhibited the myotoxicity, lethality and toxic enzymes[98]
Caseria sylvestris		Inhibited PLA2, myotoxic and hemorrhagic of crude venom[99]
Vitex negundo L. and *Emblica officinalis*	*Vipera russelli, Naja kaouthia*	Neutralized the lethal activity[100]
Parkia biglobosa	*Naja nigriollis and Echis ocellatus*	Neutralized the activity of venom[101]
Mandevilla velutina	*Bothrops and Crotalus durisus terrificus*	Neutralization of Phospholipase activity of Crotalus and partial inhibiton of Bothrops[102]
Caesaria mariquitensis	*Bothrops neuwiedi pauloensis*	Inhibited haematological and systemic alterations induced by venom[103]
Strychnus nux vomica	*Daboia russelli, Naja kaouthia*	Neutralized lethality, haemorrhage, PLA2 activity, neurotoxicity[58]
Mimosa pudica,	*Naja naja, Vipera russelli, Echis carinatus*	Anti-hyaluronidase[55]
Mimosa pudica and *Eclipta prostrate*	Malayan pit viper	Inhibited hemorrhagic activity[56]
Bixa orellena, Ficus nymphaeifolia, Struthanthus orbicularis, Gonzalagunia panamensis, Brownea rosademonte, tabebuia rosea, pleopeltis percussa, Trichomanes elegans, Renealmia alpinia, Heliconia curtispatha, Dracontium croatii and *Citrus limon*	*Bothrops asper*	Reduced edema, defibrination and coagulation effects[57]
Tabernaemontana catharinensis	*Crotalus durissus terrificus*	Inhibited the lethal activity[104]
Mandevilla illustris	*Crotalus durissus terrificus*	Inhibited the Phospholipase activity[105]
Annona senegalensis	*Naja nigricollis nigricollis*	Hyperthermia[106]

(*Contd.*)

Table 2 — List of the plants/plant extracts evaluated for their antivenom activity against various species of snakes (*Contd*.)

Mikania glomerata	*Bothrops* and *Crotalus spp*	Inhibited toxic, pharmacological and enzymatic effect of venom[107]
Pentaclethra macroloba	*Bothrops jararacussu*	Inhibited haemorrhage[108]
Croton urucurana	*Bothrops jararaca*	Inhibited the haemorrhage[109]
Cordia verbenacae	*Bothrops jararacussu*	Inhibited the paw edema[92]
Bauhinia forficata	*Bothrops and crotalus*	Inhibited the serine proteases[110]
Aristolochia odoratissima	*Bothrops atrox*	Inhibited the mortality[111]
Tabernaemontana catharinensis	*Bothrops jararacussu*	Inhibited the myotoxic effect[112]
Crinum jagus	*Echis occellatus, Bitis ariteans and Naja nigricollis*	Protected experimental animals from death, myonecrosis and haemorrhage[80]
Tamarindus indica	*Vipera russelli*	Inhibited toxic, pharmacological and enzymatic effect of venom[61]
Withania somnifera	*Naja naja*	Iinhibited the PLA2 activity[62]
Artemisia campstresis	*Macrovipera lebetina*	Neutralized venom induced actions[113]
Galactia glaucescens	*Crotalus durissus terrificus*	Inhibited neuromuscular paralysis[114]
Vitis vinifera L.	*Echis carinatus*	Neutralized Oedema, hemorrhage, myonecrosis and coagulation[90]
Azadirachta indica	*Naja naja* and *Vipera russelli*	Inhibition of PLA_2 enzymes of Cobra and Russell's Viper venoms[64]
Mimosa pudica	*Naja naja* and *Bungarus caeruleus*	Neutralization of lethality, phospholipase A_2, edema forming and hemorrhage activity[81]
Camellia sinensis	*Naja naja kaouthia* and *Calloselasma rhodostoma*	Inhibited the toxic enzymes of venom[75]
Mucuna pruriens	*Naja naja* and *Bungers caeruleus*	Neutralization of lethality, phospholipase A2, edema forming and hemorrhage activity[83]
Mangifera indica	*Vipera russelli*	Inhibited the toxic, pharmacological and enzymes of venom[72]
Piper longum	*Vipera russelli*	Pharmacological and toxic effects neutralization[87]
Ophiorrhiza mungos	*Vipera russelli*	Lethal toxicity , hemorrhage and its neutralization[89]
Bellucia dichohotoma	*Bothrops atrox*	Hemorrhage, edema, lethal toxicity neutralization by pre treatment and traditional method[115]
Pluchea indica, Hemidesmus indicus, Vitex negundo and *Emblica officinalis*	*Vipera russelli, Echis carinatus, Naja naja, Bungarus caeruleus*	Pharmacological and neutralization[116]
Euphorbia hirta	*Naja naja*	Enzyme inhibition studies, pharmacological activities neutralization[117,118]
Cyclea peltata	*Naja Naja*	*in vivo* lethality[119]
Jusitica adathoda	*Vipera russelli*	*in vitro* inhibitory activity[120]
Tamarindus indica	*Bitis arietans*	Hemolysis, anticoagulant and in vivo hemorrhagic activity[121]
Clerodendrum serratum	*Bungarus caeruleus, Daboia russelli*	*in vitro* and *in vivo* neutaliztion studies[122]
Azima tetracantha Lam.	*Vipera russelli, Bungarus caeruleus*	*in vitro* and *in vivo* neutaliztion studies[123,124]

Purified components with antiophidian properties

Enzyme inhibiting and protein binding properties have been associated with chemically active compounds of flavonoids, polyphenols, terpenoids, xanthene etc. The phytochemicals also inhibit PLA_2 activities of viper and cobra venom[125]. Phenolics especially polyphenols, like some tannins bind proteins, acting upon components of venom directly and disabling them to act on receptors. They could also act by competitive blocking of the receptors[126]. Tannic acid is found to be a potent inhibitor of hyaluronidase[127].

Pentacyclic triterpenes, betulin and betulinic acid extracted from *Betula alba* have demonstrated activity against PLA2[128]. Edunol, a pterocarpan isolated from *Harpalyce brasiliana* was found to be antiproteolytic and an inhibitor of PLA_2[129]. A triterpenoid saponin from *Gymnema sylvestre*, potassium salt of gymnemic acid inhibited the ATPase induced by *Naja naja* venom[130].

A glycoprotein WSG with a molecular mass of 27 kDa was isolated from *W. Somnifera* that inhibited the toxic PLA_2 of cobra venom[131]. Machiah *et al.* showed that the WSG completely inhibited the

hyaluronidase activity of cobra and viper venoms[62]. The peptide RW12 with a molecular mass of 6 kDa isolated from *Schmanniophyton magnificum* showed anti-cobra activity[132]. The multiform glycoprotein gpMUC isolated from the seeds of *M. Pruriens* showed immunological protection against snake venoms in victims[133].

Lupeol acetate from roots of *Hemidesmus indicus* R.Br. is documented to significantly neutralize oedema, haemorrhage and defibrinogenation induced by Russell's Viper, in experimental animals, besides the cardiotoxicity, neurotoxicity and respiratory changes induced by *Naja kaouthia* venom[60].

Eclipta prostrata is used for snake bites in China and Brazil. The aqueous extract of *Eclipta prostrata* and wedelolactone, a potent and selective 5-lipoxygenase inhibitor isolated from the plant, has shown anti-hemorrhagic activity against *Bothrops jararaca*, *Bothrops jararacussu* venoms and myotoxins, bothropstoxin and crotoxin[134,135].

Glycyrrhizin a thrombin inhibitor, from the roots of *Glycyrrhiza glabra* has shown anti-thrombotic properties *in-vivo*. Prevention of venom-induced changes in hemostasis, both *in-vivo* and *in-vitro*, have also been noted[136]. Neutralization of hemorrhagic, fibrinolytic and proteolytic activities of metalloproteases from Bothrops snake venoms is reported with a triterpenoid saponin isolated from *Pentaclethra macroloba*[137]. Ar-turmerone from *Curcuma longa* roots has shown neutralization of the lethal effect of *Crotalus durissus terrificus* and hemorrhagic effect of *Bothrops jararaca* venoms[138]. Tannic acid is documented to neutralize haemorrhage due to *Crotalus adamanteus* venom[127]. *Baccharis trimera* has yielded clerodane diterpenoid, possessing anti-hemorrhagic properties against snake venoms[139]. Some of the phytochemicals isolated with antivenom activity are listed in Table 3.

Table 3 — List of isolated constituent/s from various plants with anti-snake venom activity

Phytochemical	Plant	Antisnake venom activity
Tannic acid solution		Lethal toxicity neutralization
Tannin	*Diospyrus kaki*	Neutralized toxic effects and swelling induced by Erabu sea snake venom
Cabenegrines A-I and A-II	*Annona coriacea*	Antidote
Potassium gymnemate	*Gymnema sylvestre*	Active component inhibited *N. naja* venom and *V. russelii* venom
Schumanniofoside	*Schumanniophyton magnificum*	Inhibited lethal toxicity of *N. melanoleuca* venom by *in vitro* methods
Aristolochic acid	*Aristolochia radix*	Inhibitor of PLA_2 enzyme, oedema, direct and indirect hemolytic activity
Wedelolactone, sitosterol and stigmasterol	*Eclipta prostrata*	Inhibitedlethal toxicity induced by *Crotalus durissus terrificus* and *Bothrops jararaca, Bothrops jararacussu* and *Lachesis muta* venom-induced toxic effects and PLA_2 activity.
ar-turmerone	*Curcuma longa*	Inhibited activities of *Bothrops jararaca* venom and *Crotalus durissus terrificus* venom
Peptide	*Schumanniophyton magnificum*	Anti-cobra activity
2-hydroxy-4-methoxy benzoic acid	*Hemidesmus indicus*	Anti-inflammatory, antipyretic antioxidant, phosphatase and transaminase
Edunol	*Brongniartia podalyrioides* and *B. intermedia*	Inhibited the lethal toxicity of *Bothrops atrox*
Ehretianone	*Ehretia buxifolia*	Anti-snake venom activity against *E. carinatus*
Glycyrrhizin	*Glycyrrhiza glabra*	Thrombin inhibitor
2-hydroxy-4-methoxy benzoic acid, anisic acid, salicylic acid and aspirin	*Hemidesmus indicus*, *Pimpinella anisum*, *Filipendula ulmaria*, *Salix alba*	Inhibited *V. russelii*, *E. carinatus*, *N. kaouthia* and *Ophiophagus hannah* induced lethal, hemorrhagic and defibrinogenation
12-methoxy-4-methylvoachalotine (quaternary alkaloid)	*T. catharinensis*	Inhibited *Crotalus durissus terrificus* venom induced myotoxicity and lethality
Neo-clerodane diterpenoid	*Baccharis trimera*	Anti-proteolytic and anti-hemorrhagic properties against *Bothrops* snake venom
Melanin	*Thea sinensis* Linn.	Inhibitory effects against *Agkistrodon contortrixlaticinctus, Agkistrodon halysblomhoffii*, and *Crotalus atrox*
4-nerolidylcatechol	*Piper umbellatum and Piper peltatum*	Inhibited PLA_2 activity, myotoxic, and edema activity of Bothrops snake venom
Lupeal acetate	*Hemidesmus indicus* R.Br.	Inhibited *D. russelii* and *N. kaouthia* venom induced pharmacological activity and toxicity

(*Contd.*)

Table 3 — List of isolated constituent/s from various plants with anti-snake venom activity (*Contd*.)

Phytochemical	Plant	Antisnake venom activity
β-sitosterol and stigmasterol	*Pluchea indica*	Viper and cobra venom induced pharmacological activity
Glycoprotein (WSG)	*Withania somnifera*	PLA_2 inhibitor of *N. naja* venom
Triterpenoid saponins	*Pentaclethra macroloba*	Antiproteolytic and antihemorrhagic against *Bothrops neuwiedi* and *Bothrops jararacussu* venom
Ursolic acid		Inhibited PLA_2, oedema, indirect hemolytic activity, induced by the *V. russelii* and *N. naja* venom
Oleanolic acid		Inhibited PLA_2, edema and indirect hemolytic activity induced by the *V. russelii* and *N. naja* venom
Ellagic acid	*Casearia sylvestris*	Inhibited lethal toxicity and PLA_2 activity of *Bothrops* genus
Turmerin	*Curcuma longa* L.	Inhibited cytotoxicity, edema, myotoxicity of *N. naja* venom
AIPLAI	*Azadirachta indica*	anti- PLA_2 activity *in N. kaouthia* and *D. russelii*
Glycoprotein	*Mucuna pruriens*	Pro-thrombin inactivation from *E. carinatus* venom
Piperine	*Piper longum*	Neutralized pharmacological activity induced by Russlell viper in mice and chick embryo model
Ellagic acid, gallic acid, quinic acid and pyrogallol, 3-O-α-rhamnoside	*Euphorbia hirta*	Inhibitory potential against *N. naja*

Conclusion

The diversity of natural products provides a platform for improvisation and development of molecules that could be an aid to neutralize the effect of snakebite and associated problems. The isolation of molecules from the plants is a cumbersome process and has to undergo various assays and efficacy tests for commercial approval. Many plants have been reported to have anti-venom property; but the scientific correlation is not available. The methods and assays for the isolation and testing are to be improvised for the indigenous method of treatment to become commercially relevant. Hence, working towards the same would result in the availability of the antivenoms that are feasible and easily available to the rural and common population across the world.

Conflict of interest

The authors declare no conflict of Interest

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