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Phytopharmacology of Antiophidian Botanicals: A Review

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Abstract: Venomous snakebite has been a major cause of mortality and morbidity across the Asian, African and Latin American countries. Lack of medical infrastructure, ineffectiveness of conventional antivenin and malpractice by the local quacks worsen the scenario. The present review deals with the pharmacological investigations performed in different botanicals for antiophidian principles. It also includes a list of certain traditionally used medicinal plants with potential anti snake venom efficacy. The authors have compiled a number of plants active *in vitro* and/or *in vivo* against the toxicity of various snake venoms causing an array of biological symptoms. This review also compiles the information regarding the possible use of plant derived natural product based antivenins in order to find cheap and effective alternative source of snake venom antidote especially for the third world tropical countries. From a variety of literature sources the data has been collected mentioning the plants alphabetically and their respective families with notes on plant parts and solvent system used, *in vitro* and *in vivo* analyses, activity against the toxicity and biological symptoms related to poisonous snakebite, dose dependence, experimental models, efficacy of the isolated compound(s), ethnobotanical and clinical relevance etc.

Key words: Snakebite, pharmacology, antiophidian, ethnomedicine, phospholipase, antivenin

INTRODUCTION

Since time immemorial, plants have served as a major source of food and medicine for the mankind. Different ethnic groups use medicinal plants in the treatment of various types of ailments (Dey and De, 2010a, b; 2011a, f). They have been evaluated for a number of biologically active substances with potential therapeutic value. Different plant species have been investigated pharmacologically for antibacterial (Dey and De, 2012a), antifungal (Louis *et al*., 2011), antioxidative (Dey and De, 2012b), antifeedant (Deepa and Narmatha Bai, 2010), cytotoxic (Harliansyah *et al*., 2007), larvicidal (Raghavendra *et al*., 2011), antifertility (Shah *et al*., 2010), Immunomodulatory (Latorre *et al*., 2009), antidiabetic (Palsamy and Malathi, 2007), hepatoprotective (Dhanasekaran and Ganapathy, 2011), anti-inflammatory (Karaca *et al*., 2009), diuretic (Bala *et al*., 2011) and analgesic (Gill *et al*., 2011) properties. There are reports of using medicinal plants against snakebite by different ethnic communities throughout the world especially in the tropical and sub tropical snake prone countries of Asia, Africa and South America. Many of these ethnic uses of medicinal botanicals have been verified by *in vitro* and/or *in vivo* methods. Although the herb based alternative therapy has proven to be an exciting prospect, clinical trials and standardization are still due in order to include them in drug discovery programs (Sarwar *et al*., 2011).

Amputation and disability (Abubakar *et al*., 2010), tetanus (Habib, 2003), gangrene (Abbas *et al*., 2009), cortical necrosis of the kidneys (Varagunam and Panabokke, 1970; Date and Shastry, 1981) etc., are among the medical manifestations of snakebite. First aid and care of the snakebite victims (Saul *et al*., 2011; Rushing, 2011) and treatment of pediatric victim (Cordasco *et al*., 2001) are also among the important aspects of post snakebite measures. Lack of medical infrastructure in the rural areas, ignorance, side effects of animal based antivenins etc. necessitate the development of alternative therapy of snake bite. Due to higher risk of mortality in this medical exigency and the limitations associated with using conventional antivenom immunotherapy, a number of medicinal plants with antiophidian principles have been investigated in order to achieve an alternative system of anti venin therapy.

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An array of enzymatic reactions is involved with the snake bite. Enzymes such as Phospholipase A2 (PLA2), protease, hyaluronidase, 5'nucleotidase, ATPase, alkaline phosphomonoesterase etc., have been reported to be associated with snake venom causing a number of biological symptoms such as hemorrhage, haemolysis, defibrinogenation, inflammation, edema, necrosis, proteolysis, cardiotoxicity, myotoxicity, myonecrosis, neurotoxicity, pro-coagulation, anti-coagulation and lethality (Soares *et al*., 2005). Inhibition of PLA2, one of the active constituents of snake venoms has been studied by using a number of natural and artificial biomolecules (Alcaraz and Hoult, 1985; Lindahl and Tagesson, 1997; Faure, 2000; Lizano *et al*., 2003; Marcussi *et al*., 2007; Nirmal *et al*., 2008; Hage-Melim *et al*., 2009).

Investigators have tried to find out scientific basis of certain plants' use as antiophidian ethnomedicine. Most of these anti venom efficacy testing have been performed *in vitro* on isolated venom enzymes and toxins and *in vivo* in experimental animals. Some of the plant extracts were found to have potency as antivenin *in vitro* but failed to show venom neutralizing ability *in vivo*. Some investigators were able to isolate the antiophidian compound by fractionation and purification. In certain experiments, scientists were unable to find any antiophidian principle from some plants having a wide range of use as anti snake venom traditional medicine. A few authors have suggested the possibility of using certain plant extract or the isolated compound as an alternative of conventional antivenin. However, proper clinical trial must be performed in order to approve such alternative therapy in medical exigencies like snakebite.

Antiophidian ethnobotany: Aboriginal and indigenous people have always been a valuable resource of knowledge on medicinal plants. Ethno-ophiology describes the ethnic people's knowledge involving snakes (Joshi and Joshi, 2010). Snakelores and snakebite antidotes are integral parts of indigenous practices (Jain *et al*., 2011). Traditional use of herbs against snakebite by the local medical practitioners, snake charmers and ethnic people is a common practice in rural parts of the third world due to inadequate medical infrastructure and source of antivenin. Traditional use of antiophidian botanicals have been investigated especially in the snake prone rural south east Asian, African and Latin American countries (Jain and Tarafder, 1963; Siddiqui and Husian, 1990; Pereira *et al*., 1994; Mebs, 2000; Otero *et al*., 2000a, b, c; Nunez *et al*., 2004; Owuor *et al*., 2005; Samy *et al*., 2008; Panghal *et al*., 2010; Dey and De, 2011d, 2012c).

Herbs against snakebite: Use of herbs has always been a popular remedy against snakebite. These medicinal plants having antagonistic efficacy against snakebite have been evaluated pharmacologically and several active components have been isolated having snake venom neutralization capacity (Morris, 1887; Liang, 1987; Rizzini *et al*., 1988; Mors, 1991; Mors *et al*., 2000; Martz, 1992; Selvanayagam *et al*., 1994, 1995; Houghton and Osibogun, 1993; Houghton and Skari, 1994; Alam and Gomes, 1996; Wang *et al*., 1997; Yang *et al*., 1998; Soares *et al*., 2005; Daduang *et al*., 2005; Owuor and Kisangau, 2006; Sanchez and Rodriguez-Acosta, 2008; Nishijima *et al*., 2009; Gomes *et al*., 2010; De Paula *et al*., 2010; Ibrahim *et al*., 2011).

Potential antiophidians: Although, many of the antiophidians have been investigated pharmacologically, a large number of medicinal plants traditionally used against snake bite are yet to be evaluated. *Rauvolfia serpentina* (Dey and De, 2010c, 2011b), *Achyranthes aspera* (Dey, 2011a), *Alstonia acholaris* (Dey, 2011b), *Aristolochia tagala* (Dey and De, 2011c), *Amaranthus viridis*, *Acorus calamus*, *Calotropis procera*, *Cassia fistula*, *Cissampelos pareira*, *Clitoria ternatea*, *Boerhaavia diffusa* (Dey and De, 2012c) are among the very popular antiophidian ethnomedicinal plants particularly used in the Indian subcontinent. Although various reports are present on phytochemical constituents and pharmacological efficacy of the plants, these are yet to be evaluated pharmacologically for anti snake venom activity or constituents. Therefore, laboratory based evidence is required to analyze the scientific basis of the folk practice. Further study on these botanicals may generate some novel compounds as candidates for natural plant based antivenin complementing the conventional snake bite treatments.

Antiophidian compounds: Vanillic acid (4-hydroxy-3-methoxybenzoic acid) (Dhananjaya *et al*., 2006); Terpenoid saponins such as macrolobin-A and B (Da Silva *et al*., 2007); polyphenols (Leanpolchareanchai *et al*., 2009a; Mahadeswaraswamy *et al*., 2011); ellagic acid (Da Silva *et al*., 2008); rosmarinic acid (Ticli *et al*., 2005); aristolochic acid (8-methoxy-6-nitrophenanthro[3,4-*d*][1,3]dioxole-5-carboxylic acid) and quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) (Girish and Kemparaju, 2005); Glycyrrhizin (Assafim *et al*., 2006); Lupeol acetate (Chatterjee *et al*., 2006); 2-hydroxy-4-methoxy benzoic acid (Alam and Gomes, 1998a, b); A pthalate (Sarkhel *et al*., 2011); Tannin (Ambikabothy *et al*., 2011); Beta sitosterol, stigmasterol

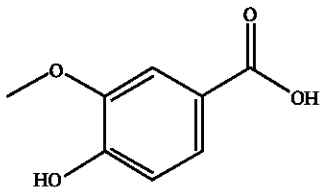

Fig. 1: Vanillic acid (4-hydroxy-3-methoxybenzoic acid)

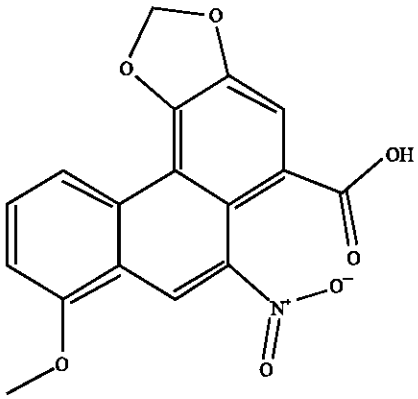

Fig. 2: Aristolochic acid (8-methoxy-6-nitrophenanthro [3,4-d][1,3]dioxole-5-carboxylic acid)

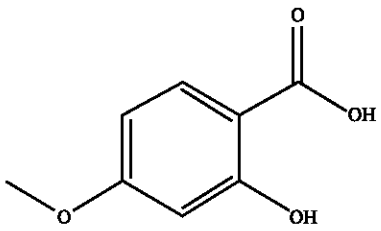

Fig. 3: 2-Hydroxy-4-methoxy benzoic acid

(Gomes *et al*., 2007); Wedelolactone (1,8,9-trihydroxy-3-methoxy-6H- [1] benzofuro[3,2-c] chromen-6-one) (Melo *et al*., 1993); Turmerin (Chethankumar and Srinivas, 2008); heparin and para-bromophenacyl bromide (Melo and Ownby, 1999) etc. have been investigated for antiophidian properties. Figure 1 to 9 denotes the structures of some of the antivenin compounds. Although, this article mainly focuses on the reports on botanicals active pharmacologically against snakebite, (Mors *et al*., 2000; Soares *et al*., 2005; Gomes *et al*., 2010) have given a list of biologically active compounds as antivenoms or having potential antivenin efficacy.

Enumeration: The plants are arranged alphabetically with their respective families. In addition to that, notes on plant parts and solvent system used, *in vitro* and *in vivo* analyses, activity against the venom toxicity and biological symptoms related to poisonous snakebite, dose

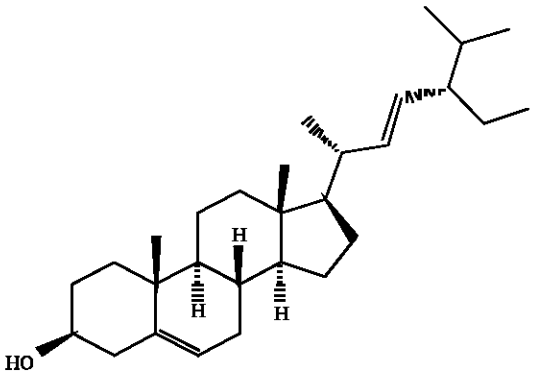

Fig. 4: Stigmasterol (3S,8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol)

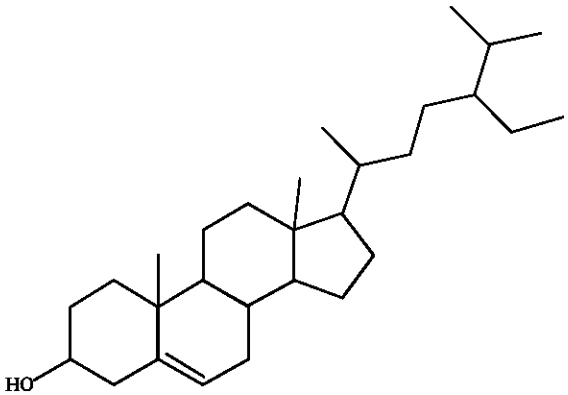

Fig. 5: Beta sitosterol (17-(5-ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[*a*]phenanthren-3-ol)

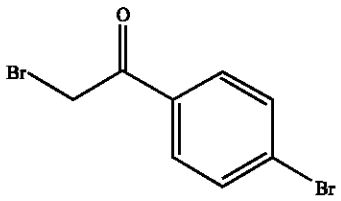

Fig. 6: Para-bromophenacyl bromide

dependence, experimental models, efficacy of the isolated compound(s), ethnobotanical and clinical relevance etc., have also been compiled. It was noted that most of the reports have been recorded from the tropical Asian (Indian subcontinent), African (Nigeria) and Latin American (Brazil) countries where the traditional plant based snakebite remedies have been evaluated scientifically.

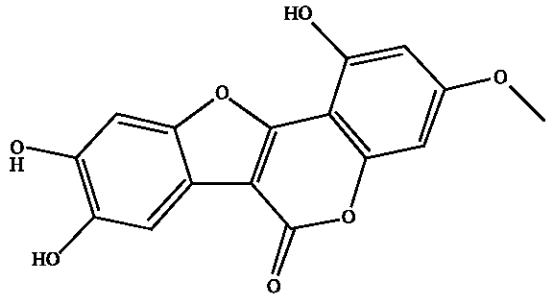

Fig. 7: Wedelolactone (1,8,9-trihydroxy-3-methoxy-6H-[1]benzofuro[3,2-c]chromen-6-one)

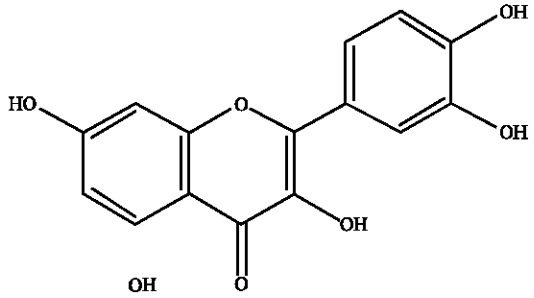

Fig. 8: Quercitin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one)

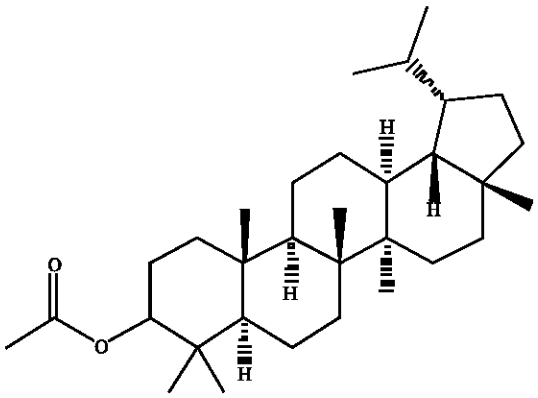

Fig. 9: Lupeol acetate

Algae: *Naja nigricollis* venom has been effectively neutralized by the extracts of the alga *Padina boergesenii* and *Hypnea valentiae in vitro* (Vasanthi *et al*., 2003). Hemolytic activity of *Lachesis muta* snake venom was found be inhibited by a diterpene isolated from the brown alga *Canistrocarpus cervicornis* (Moura *et al*., 2010).

Angiosperms

***Acalypha indica* L. (family: Euphorbiaceae):** Lethality, haemorrhage, necrotizing and mast cell degranulation effects of *Vipera russelli* venom in rats and the cardiotoxicity and neurotoxicity in isolated frog tissue were inhibited by the ethanol leaf extract in a dose dependent manner (Shirwaikar *et al*., 2004).

***Anacardium occidentale* L. (family: Anacardiaceae):** Anti-phospholipase, anti protease and anti-hyaluronidase activities of the bark extract were exhibited against the hydrolytic enzymes of the *Vipera russelii* venom. The extract has also neutralized the venom induced edema, hemorrhagic, myotoxicity, myonecrotic and inflammatory effects (Ushanandini *et al*., 2009).

***Andrographis paniculata* (Burm. f.) Wall. ex Nees (family: Acanthaceae):** Extract form the plant has prevented cobra venom induced death in mice while administered in a particular dose (Nazimuddin *et al*., 1978). Methanolic extract of the plant has exhibited neutralization of *Daboia russelli* venom and prevented toxicity and lethality of the venom action (Meenatchisundaram *et al*., 2009a,b).

***Annona senegalensis* Pers. (family: Annonaceae):** Methanol extracted root bark of this Nigerian ethnomedicinal plant was found to inhibit *Naja nigricollis nigricollis* venom induced mortality, toxicity and enzymatic activity in experimental models (Adzu *et al*., 2005).

***Aristolochia* sp., (family: Aristolochiaceae):** *Vipera russelli* PLA2 was neutralized by direct uncompetitive inhibitor by aristolochic acid, an alkaloid form *Aristolochia* sp. The compound has also shown anti-edema activity of PLA2 (Vishwanath and Gowda, 1987). In addition to that, interaction between the inhibitor and the venom was studied by circular dichroism. A change was noted in the secondary structure of the enzyme (Vishwanath *et al*., 1987a).

***Aristolochia indica* L.:** *A. indica* is one of the few medicinal plants having extensive use as antiophidian ethnomedicine. The plant has been tested pharmacologically for anti snake venom activities (Dey and De, 2011e). *Daboia russelli* venom induced lethality was neutralized by methanolic extract of the plant which showed anti- hemorrhagic, anti-edema, anti-fibrinolytic activity (Meenatchisundaram *et al*., 2009a). Inflammatory, analgesic and pyretic responses of *Heteropneustes fossilis* were neutralized by dried plant extract in a dose dependent manner in rats (Das *et al*., 2010).

***Aristolochia radix*:** Interaction between aristolochic acid from *Aristolochia radix* and three PLA2 from *Trimeresurus flavoviridis* snake venom has also been

reported (Vishwanath *et al*., 1987b). Aristolochic acid from *A. radix* was found to inhibit some Formosan snake venom *in vivo* (Tsai *et al*., 1980).

***Aristolochia albida* Duch.:** Inhibitory effect on anti-coagulant, hemolytic and PLA activities of *Naja nigricollis* venom by *Aristolochia albida* methanolic extract was noted (Abubakar *et al*., 2006).

***Azadirachta indica* A. Juss. (family: Meliaceae):** AIPLAI (*Azadirachta indica* PLA(2) inhibitor), a compound from the methanolic extract of leaf was found to inhibit PLA2 enzymes of cobra and Russell's viper (Mukherjee *et al*., 2008).

***Baccharis trimera* (less.) DC. (family: Asteraceae):** A compound isolated from the Brazilian plant was found to inhibit the hemorrhagic and proteolytic activities of *Bothrops* snake venoms. The compound has also exhibited neutralizing ability against class P-I and III metalloproteases isolated from *B. neuwiedi* and *B. jararacussu* venoms by showing anti- hemorrhagic, anti-fibrinogenolytic and anti-caseinolytic activities (Januario *et al*., 2004).

***Bauhinia forficata* Link (family: Fabaceae):** Aqueous extract of the aerial plants were assayed against coagulant and fibrinogenolytic activities of *Bothrops jararacussu* and *Crotalus durissus terrificus* crude venoms. The extract has also exhibited anti-edema activity against *C. durissus terrificus* venom. However, the extract did not show any anti-hemorrhagic activity against the *Bothrops* venom (Oliveira *et al*., 2005).

***Blutaparon portulacoides* (A. St.-Hil.) mears (family: Amaranthaceae):** Ethanolic extract of the aerial part has shown anti-inflammatory activity induced by *Bothrops jararacussu* venom. The extract has also exhibited anti-myotoxic effect against isolated BthTX-I and II myotoxins (Pereira *et al*., 2009).

***Brongniartia podalyrioide* kunth (family: Fabaceae):** A prenylated pterocarpan named (-)-Edunol was found having antagonistic effect against *Bothrops atrox* venom (Reyes-Chilpa *et al*., 1994).

***Calotropis gigantea* (L.) R. Br. (family: Apocynaceae):** Procoagulent and fibrinolytic activities of the latex (Rajesh *et al*., 2005) can be exploited as a natural antivenin against poisonous snakes.

***Camellia sinensis* (L.) Kuntze/*Thea sinensis* L. (family: Theaceae):** Fresh leaves of *C. sinensis* extracted in methanol has shown inhibitory effect against *Naja naja kaouthia* Lesson (Elapidae) and *Calloselasma rhodostoma* Kuhl (Viperidae) venoms. The antivenin potential could have been mediated by phenolic content present in the extract (Pithayanukul *et al*., 2010). Melanin extracted from black tea (*T. sinensis*) has exhibited antagonistic activity in mice against *Agkistrodon contortrix laticinctus* (broadbanded copperhead), *Agkistrodon halys blomhoffii* (Japanese mamushi) and *Crotalus atrox* (western diamondback rattlesnake) snake venoms in a dose dependent manner (Hung *et al*., 2004).

***Casearia sylvestris* Sw. (family: Salicaceae):** The crude aqueous extract of the leaves has shown prolific anti-PLA2 activity against several Brazilian snake venoms and also against different classes of isolated PLA2s. Anti-coagulant, anti-edema and anti-myotoxic activities have been contributed by the extract either against the venom or the purified compounds. The plant may serve as a potent source of PLA2 inhibitors (Borges *et al*., 2000). Crude extracts and pure compounds from the plant have exhibited anti PLA2 activity against snake venoms and purified toxins. They have also shown anti-hemorrhagic and anti-myotoxic activities (Raslan *et al*., 2002). *Bothrops* and *Crotalus* venoms and purified PLA2s were found to be neutralized by aqueous extracts. Neuromuscular blockade and muscle damage caused by the venom toxin were significantly neutralized by the herbal extract (Cavalcante *et al*., 2007). In addition, ellagic acid and ellagic acid derivatives have been isolated from the aqueous extract. Ellagic acid has given the best results as anti- edematogenic and anti-myotoxic agent. Depending on the position of hydroxyl and methoxyl groups, the anti venom efficacy of the derivatives were found to vary. Folk use of the plant as an antiophidian is being supported by the studies (Da Silva *et al*., 2008). Hydroalcoholic extract of this Brazilian ethnobotanical was found to inhibit neuromuscular blockade of the myotoxic bothropstoxin-I from *Bothrops jararacussu* snake venom (Oshima-Franco *et al*., 2005). Polar and non polar parts of the leaf extract have shown same kind of activity whereas the methanolic extract has exhibited maximum activity (Cintra-Francischinelli *et al*., 2008).

***Cissampelos pareira* L. (fmily: Mnispermaceae):** Anti-hemorrhagic and anti-proteolytic activities against *Bothrops asper* venom was shown by an extract of the plant (Badilla *et al*., 2008).

***Cordia verbenacea* DC. (fmily: Braginaceae):** Rosmarinic acid isolated from the methanolic extract of the plant from Brazil was found to be a potent inhibitor of PLA2.

Bothrops jararacussu venom and its component PLA2 toxins were inhibited to varying degree by the compound having anti-inflammatory and anti-myotoxic properties. Higher level of inhibition was noted against the basic PLA2s (Ticli *et al*., 2005).

***Crinum jagus* (Tompson) Dndy (fmily: Amaryllidaceae):** *In vitro* and *in vivo* antiophidian efficacy of the methanolic extract of the bulb has been investigated against *Echis ocellatus*, *Bitis arietans* and *Naja nigricollis* venoms. The experimental models were either given the extract orally prior to injection of the venom or the pre-incubated mixture of extract and venom were administered. In both the cases, the results were almost similar. Lethality, myonecrotic and haemorrhagic actions of the Nigerian snake venoms have been significantly neutralized by the extract (Ode and Asuzu, 2006).

***Curcuma* sp., (family: Zingiberaceae):** *Curcuma* species was found to inhibit *Naja naja siamensis* neurotoxin. The plant's proteolytic activity was not found to be responsible for the inhibition (Cherdchu and Karlsson, 1983). The water insoluble fraction of the rhizome extract was found to contain the inhibitor (Ratanabanangkoon *et al*., 1993).

***Curcuma longa* L.:** Anti venom potential of ar-turmerone from *C. longa* has been reported (Ferreira *et al*., 1992). A 14kDa protein, Turmerin form *C. longa* has shown anticytotoxic, anti edema and antimyotoxicity against multitoxic PLA2 of *Naja naja* (Chethankumar and Srinivas, 2008).

***Curcuma zedoaroides* A. Chaveerach and T. Tanee:** The plant from the north-eastern part of Thailand was assessed for any antagonism against King cobra venom *in vitro* and *in vivo*. The extraction and purification have revealed the presence of a C_{20} dialdehyde responsible for antivenin efficacy of the plant (Lattmann *et al*., 2010).

***Dipteryx alata* vogel (family: Fabaceae):** Neurotoxicity and myotoxicity of *Bothrops jararacussu* venom were found to be decreased by the methanolic extract of the bark. The neutralizing ability could have been due to tannins present in the said extract. Bark extracted in dichloromethane also inhibited the venom activity. Phenolic acids, terpenoids, flavonoids could have been the other factors present in the extracts having snake venom neutralizing ability (Nazato *et al*., 2010). Upon chemical analysis, the extracts with antiophidian activity against *Bothrops jararacussu* venom have revealed lupane-type triterpenoid, isoflavonoid, chalcone, aurone and phenolic compounds (Puebla *et al*., 2010).

***Eclipta alba* (L.) Hassk. (family: Asteraceae):** Natural plants collected from Botucatu and Ribeirao Preto, Brazil and genetically modified plants by *Agrobacterium rhizogenes* have been tested for antiophidian efficacy against *Crotalus durissus terrificus* and *Bothrops jararacussu* venoms. Aerial parts and root extracts as well as isolated coumestans have been investigated for anti-PLA2 activity (Diogo *et al*., 2009).

***Eclipta prostrata* L. (Family: Asteraceae):** Aerial parts extracted in ethanol have shown antagonistic effect against South American rattlesnake (*Crotalus durissus terrificus*) venom in mice model. Isolated wedelolactone, sitosterol and stigmasterol have also shown to prevent lethality of the venom in a dose dependent manner. Pre-incubation of the venom with the extract prior to the injection had shown its ability *in vivo* to antagonize myotoxicty of the venom action (Mors *et al*., 1989). Efficacy of the plant extract and isolated active constituents against crotalid venoms (*Bothrops jararaca*, *B. jararacussu* and *Lachesis muta*) was also investigated supporting its use against crotalid envenomation in Brazil (Melo *et al*., 1989, 1994). Butanolic extract was investigated against *Calloselasma rhodostoma* (Malayan pit viper) and produced positive results to combat the venom action (Pithayanukul *et al*., 2004).

***Emblica officinalis* Gaertn. (family: Euphorbiaceae):** Lethality of *Vipera russellii* and *Naja kaouthia* venom was significantly neutralized by root extract of the plant *in vitro* and *in vivo*. Further investigation was suggested to explore its antiophidian principles (Alam and Gomes, 2003). Root extract of the plant was found to contain Pthalate having viper and cobra venom neutralizing potential. The compound has shown anti-hemorrhagic, anti-defibrinogenating, anti-inflammatory, anti-PLA2, anti-cardiotoxic, anti-neurotoxic and anti-myotoxic activity against the venom (Sarkhel *et al*., 2011).

***Fagonia cretica* L. (family: Zygophyllaceae):** Leaves and twigs extracted in methanol were reported as anti-haemorrhagic in a dose dependent manner against *Naja naja karachiensis* (black Pakistan cobra) venom. Anti venom efficacy of the plant was comparable to the standard antiserum (Razi *et al*., 2011).

***Guiera senegalensis* (J.F. Gmel.) (family: Combretaceae):** Venoms of *Echis carinatus* and *Naja nigricollis* from northern Nigeria have been investigated with leaf extracts of the plant *in vitro*. Intra-peritoneal administration of reconstituted venom and the extract in albino mice has produced positive results (Abubakar *et al*., 2000). Leaf

extract of the plant was tested against venom enzymes of *E. carinatus* (Sallau *et al*., 2005).

***Harpalyce brasiliana* Benth. (family: Fabaceae):** Edunol, a pterocarpan, originally isolated from this Brazilian medicinal plant was synthesized and the compound has shown anti-myotoxic, anti-proteolytic and anti PLA2 activity against snake venom (Da Silva *et al*., 2004).

***Heliconia* sp., (family: Heliconiaceae):** Ultrasound pretreated ethanolic extract were incubated with *Bothrops asper* venom and showed increased antiophidian potential than the untreated set. Ultrasound might have enhanced the amount of antiophidics in the media (Estrada *et al*., 2010).

***Hemidesmus indicus* (L.) R. Br. (family: Apocynaceae):** An organic acid (HI-RVIF) isolated from the plant had shown antagonistic effect against viper venom in rodents. The compound was isolated, purified and characterized partially and was found to be anti-haemorrhagic and anti-coagulant against viper venom (Alam *et al*., 1994). Antagonistic activity of the methanolic extract was noted against *Vipera russellii* venom (Alam *et al*., 1996). 2-hydroxy-4-methoxy benzoic acid isolated from the methanolic root extract had shown anti-inflammatory activity induced by *Vipera russelli* venom. Its antiophidian activity might also be mediated by its antipyretic and antioxidant activities (Alam and Gomes, 1998a). The purified compound has shown adjuvant and antiserum activities and significant snake venom neutralization capacity in experimental models (Alam and Gomes, 1998b). The root extract has yielded another compound, lupeol acetate which neutralized lethality and toxicity of *Daboia russellii* and *Naja kaouthia* venoms in animals. It has shown anti-haemorrhage, anti-defibrinogenation, anti-edema, anti-PLA2 activities and prevented carditoxic and neurotoxic effects of the venom (Chatterjee *et al*., 2006).

***Hibiscus aethiopicus* L. (family: Malvaceae):** Anti snake venom efficacy of the plant was demonstrated against *Echis ocellatus* and *Naja n. nigricollis* snake venoms. Positive results have indicated the presence of a possible endogenous inhibitor in the plant giving protection to the haemorrhage induced by the venom (Hasson *et al*., 2010).

***Hypericum brasiliense* choisy (family: Hypericaceae):** *In vitro* and *in vivo* efficacy of the plant was noted when tested against some Brazilian snake venoms (Assafim *et al*., 2011).

***Indigofera pulchra* Willd. (family: Fabaceae):** Inhibitory effect against the anti-coagulant, hemolytic and PLA activities of *Naja nigricollis* venom by the methanolic extract was noted (Abubakar *et al*., 2006).

***Mandevilla illustris* (Vell.) Woodson (family: Apocynaceae):** Subterranean system extracted in water has shown anti enzymatic and anti-toxic activities against *Crotalus durissus terrificus* snake venom. The crude extract has also shown activities against the isolated crotoxin and basic PLA2 of the venom (Biondo *et al*., 2004).

***Mandevilla velutina* K. Schum. (family: Apocynaceae):** The species from Brazilian savannah was investigated against *Crotalus durissus terrificus* venom and purified toxins. The efficacy of the crude aqueous extract has also been investigated against *Bothrops jararacussu*, *B. alternatus*, *B. moojeni* and *B. pirajai* snake venoms. It has shown antifibrinogenolytic, anti-caseinolytic, anti-edema-inducing and anti-myotoxic activities against various venoms in a dose dependent manner. A micropropagted plant had shown partial activity against the venom and toxins (Biondo *et al*., 2003).

***Mangifera indica* L. (family: Anacardiaceae):** Aqueous extract of stem bark had shown anti-myotoxicity of *D. russellii* venom. *In vitro* PLA2 activity of the venom was totally inhibited by the extract. Several enzymes associated with envenomation were also inhibited significantly supporting its traditional antiophidian use (Dhananjaya *et al*., 2011). Ethanolic extract of seed kernel of Thai mango (*Mangifera indica* L. cv. 'Fahlun') has shown to inhibit caseinolytic and fibrinogenolytic activities of Malayan pit viper and Thai cobra venoms *in vitro*. The phenolic constituent of the plant, pentagalloyl glucopyranose has also prevented enzymatic activities and necrotic effects of the snake venom in a dose dependent manner. Anti-snake venom metalloproteinase activity was also exhibited (Pithayanukul *et al*., 2009). *Calloselasma rhodostoma* and *Naja naja kaouthia* venoms were inhibited *in vivo* by the anti-hemorrhagic and anti-dermonecrotic properties of the ethanolic extract of seed kernel of Thai mango. Molecular docking studies were performed to explore the mechanism of action of the phenolic compound (Leanpolchareanchai *et al*., 2009b).

***Marsypianthes chamaedrys* (Vahl) Kuntze (family: Lamiaceae):** The extract has shown to neutralize fibrinoclotting activity of various Brazilian snake venoms *in vitro* (Castro *et al*., 2003).

***Mikania glomerata* Spreng. (family: Asteraceae):** Dried and fresh roots, stems and leaves extracted in water had shown different levels of activity against a number of snakes such as *Bothrops altenatus*, *B. moojeni*, *B. neuwiedi*, *B. jararacussu* and *Crotalus durissus terrificus*. Anti PLA(2). Anti edema and anti-clotting activities of the extracts were noted against the venom (Maiorano *et al*., 2005). The plant, traditionally reported as an antiophidian has been pharmacologically evaluated (Napimoga and Yatsuda, 2010). The potential of leaf extract in combination with anti-venom serum against *Crotalus durissus* venom has been evaluated in experimental rats (Floriano *et al*., 2009).

***Mimosa pudica* L. (family: Fabaceae):** Dried roots extracted in alcohol and water were found to inhibit the lethality and myotoxicity of *Naja kaouthia* venom (Mahanta and Mukherjee, 2001). Hyaluronidase and protease activities of the venoms of some Indian snakes (*Naja naja*, *Vipera russelii* and *Echis carinatus*) were found to be inhibited by the root extracted in water (Girish *et al*., 2004). Tannin isolated from the roots has been tested *in vitro* and *in vivo* against *N. kaouthia* venom in animal model. The findings yielded positive results *in vitro* but *in vivo* investigations did not support its use as a possible antiophidian ethnomedicine (Ambikabothy *et al*., 2011). In another study, extract of the plant and its active fraction have shown inhibitory activity against *Naja naja kaouthia* venom. It has also exhibited activity against *Ophiophagus hannah*, *Bungarus candidus*, *B. fasciatus* and *Calloselasma rhodostoma* venoms (Vejayan *et al*., 2007). Root extract was found to show antitoxic effect against *Naja naja* and *Bangarus caerulus* venoms (Meenatchisundaram *et al*., 2009b).

***Morus alba* L. (family: Moraceae):** *In vitro* proteolytic and hyaluronolytic activities of the Indian *Daboia russelii* venom were completely inhibited by leaf extract of the plant. In addition, the extract has shown anti-fibrinogenolytic activity making it a prospect for anti venom therapy (Chandrashekara *et al*., 2009).

***Mucuna puriens* (L.) DC. (family: Fabaceae):** Aqueous extract of the seeds has shown anti-myotoxic, anti-cytotoxic and anticoagulation activities against *Echis carinatus* venom (Aguiyi *et al*., 2001). Effect of the extract on prothrombin activation by *E. carinatus* venom was also recorded (Guerranti *et al*., 2001). Later on, the cross reactivity between the plant protein and the venom enzymes has been studied (Guerranti *et al*., 2002). In a further study, it was revealed that a glycoprotein with functional oligosaccharide chains has been functional to provide antivenin activity (Guerranti *et al*., 2004). Pathophysiological effects of antisnake venom activity of the plant extract were analyzed by proteomics (Guerranti *et al*., 2008). Effective and moderate *in vitro* neutralization against *Naja sputatrix* and *Calloselasma rhodostoma* snake venoms were noted, respectively (Tan *et al*., 2009). Histopathological changes induced by *N. sputatrix* venom such as changes in heart and liver blood vessels were prevented in seed extract pretreated rats exposed to the venom (Fung *et al*., 2009). Seed extract was tested against *N. sputatrix* (Javan spitting cobra) venom in rats and was reported as cardiorespiartory protective and against neuromuscular depressant properties of the venom (Fung *et al*., 2011). The cardioprotective efficacy against lethality and toxicity of the venom action was found to be direct without involving blood vessel contraction. The results justify its widespread use as a traditional antiophidian botanical in Nigeria (Fung *et al*., 2012).

***Musa paradisiaca* L. (family: Musaceae):** The extract has shown Anti-PLA2, anti-myotoxic, anti-hemorrhagic anti-lethality against crotalidae venoms *in vitro* but was did not exhibit protection *in vivo* (Borges *et al*., 2005).

***Parkia biglobosa* (Jacq.) Benth. (family: Fabaceae):** Water-methanol extract of *P. biglobosa* stem bark had produced anti-cytotoxic, anti haemorrhagic activity of various snake venoms in experimental animal models. The snakes used in the experiments were *Naja nigricollis* and *Echis ocellatus*. The results supported the plants popular use in Nigeria (Asuzu and Harvey, 2003).

***Pentaclethra macroloba* Willd. Kuntze (family: Fabaceae):** Aqueous extract of this Brazilian ethnomedicinal plant has shown anti myotoxic, anti lethality, anti edema and anti PLA activities against snake venoms (Da Silva *et al*., 2005). Macrolobin-A and B were found to inhibit proteolytic and hemorrhagic activities of *Bothrops neuwiedi* and *B. jararacussu* venoms (Da Silva *et al*., 2007).

***Piper* sp., (family: Piperaceae)**
***Piper umbellatum* L. and 45. *Piper peltatum* L.:** Myotoxic activity of PLA2 from *Bothrops* snake venoms was found to be inhibited by the plant extracts. The active compound isolated was 4-nerolidylcatechol (Nunez *et al*., 2005).

***Pluchea indica* (Less) (family: Asteraceae):** Coagulant and anticoagulant activity and lethality induced by

Vipera russellii venom were found to be neutralized by the methanolic root extract (Alam *et al*., 1996). Two plant sterols such as beta-sitosterol and stigmasterol from the root extract had shown significant efficacy against viper and cobra venom in terms of anti-haemorrhage, anti-defibrinogenation, anti-edema, anti-PLA2 activities and carditoxic and neurotoxic effects were antagonized by the compounds in experimental animals. The two plant derived sterols and antiserum together might have played a significant role as antiophidians (Gomes *et al*., 2007).

***Pouzolzia indica* (L.) Gaudich. (family: Urticaceae):** Alcoholic and aqueous extracts have exhibited snake venom neutralizing ability against Russell viper venom (Ahmed *et al*., 2010).

***Schizolobium parahyba* (Vell.) S.F. Blake (family: Fabaceae):** Anti PLA2, anticoagulant, anti-fibrinogenolytic, anti-hemorrhagic and anti-myotoxic efficacy of the aqueous leaf extracts of the plant from Mata Atlantica in Southeastern Brazil have been reported against *Bothrops pauloensis* and *Crotalus durissus terrificus* venoms and their various toxins (Mendes *et al*., 2008). Furthermore, lethality, blood incoagulability, haemorrhagic and indirect haemolytic activities of *Bothrops alternatus* and *B. moojeni* venom were neutralized by the extract whereas it has shown anti-fibrinogenolytic property against *B. alternatus* venom. Methanolic fraction of the extract has produced maximum efficacy. It was concluded that the extract and tannin could have been responsible for antiophidian efficacy (Vale *et al*., 2008).

***Schumanniophyton magnificum* (K. Schum.) Harms (family: Rubiaceae):** When the stem and root barks of the plant were extracted in mathanol and the polar fraction was analyzed against cobra venom cardiotoxin *in vitro*, activity was noted (Houghton and Harvey, 1989). Furthermore, aqueous extract of the bark has yielded a 600 daltons peptide having dose dependent antagonistic activity against cardiotoxin and total venom of cobra species in animal model (Houghton *et al*., 1992). The methanloic stem bark extract and a chromone alkaloidal glycoside schumanniofoside isolated from the extract inhibited the lethality of black cobra (*Naja melanoleuca*) venom in mice. Oxidative inactivation of the venom by the active compound might have been responsible for the inactivation (Akunyili and Akubue, 1986).

***Tabernaemontana catharinensis* A. DC. (family: Apocynaceae):** Lethality and myotoxicity of South American rattlesnake (*Crotalus durissus terrificus*) venom was neutralized in a dose dependent manner by the lyophilized aqueous extract and an alkaloid 12-methoxy-4-methylvoachalotine isolated from a fraction of the ethanolic extract of the plant. Terpenes and sterols have been isolated from other fractions of the extract. The findings have shown evidences of its tribal antiophidian use as a Brazilian folk plant (Batina *et al*., 2000). Fractions obtained by gel filtration have also shown anti-crotalic activity (De Almeida *et al*., 2004). In addition, anti-myotoxic effect of the aqueous extract has also been reported against *Bothrops jararacussu* venom and its component myotoxins (Veronese *et al*., 2005).

***Tamarindus indica* L. (family: Fabaceae):** An array of hydrolytic enzymes for envenomation of *V. russelli* was found to be inhibited by seed extract of the plant. Edema, hemorrhage, myotoxicity and lethality were greatly neutralized in a dose dependent manner (Ushanandini *et al*., 2006).

***Vitex negundo* L. (family: Lamiaceae):** *Vipera russellii* and *Naja kaouthia* snake venom lethality was significantly neutralized by root extract of the plant *in vitro* and *in vivo* (Alam and Gomes, 2003).

***Vitis vinifera* L. (family: Vitaceae):** Methanolic extract of grapes seeds was tested against Indian *Echis carinatus* (saw-scaled viper) venom. The extract has shown anti-edema, anti-haemorrhagic, anti-myonecrotic and pro-coagulant effect as well as anti-caseinolytic, anti-hyaluronolytic and anti-fibrinogenolytic activities (Mahadeswaraswamy *et al*., 2008). Further, the extract was investigated against the Indian *Daboia/Vipera russelli* venom. Proteolytic and hyaluronidase activities of the venom were completely inhibited whereas hemorrhage, edema-inducing and myonecrotic activities were greatly reduced. The extract has also shown potent anti-defibrinogenation activity and partial pro-coagulant property (Mahadeswaraswamy *et al*., 2009).

***Withania somnifera* (L.) Dunal (family: Solanaceae):** A 27kDa PLA inhibitor was isolated from the plant having anti-cytotoxic, anti-edema and anti-myotoxic activity against the Indian cobra venom PLA. The action was mediated by forming a complex between the inhibitor glycoprotein and the PLA (Deepa and Gowda, 2002). Anti-hyaluronidase activity of the inhibitor against *Naja naja* and *Daboia russelii* venoms has also been reported. These findings support the plants use as an antidote in rural India (Machiah *et al*., 2006). A neurotoxic PLA2 purified from Indian cobra *Naja naja* venom was also inhibited by the same compound (Machiah and Gowda, 2006).

DISCUSSION

The authors have compiled reports on 3 alga and 54 angiosperms evaluated pharmacologically against isolated snake venom *in vitro* or *in vivo* in different experimental animals. Maximum number of investigations was performed in *Aristolochia* sp., *Casearia sylvestris*, *Curcuma* sp., *Eclipta prostrata*, *Hemidesmus indicus*, *Mangifera indica*, *Mikania glomerata*, *Mimosa pudica*, *Mucuna puriens*, *Schumanniophyton magnificum*, *Tabernaemontana catharinensis* and *Withania somnifera*. It is worth to note that most of these species are potent ethnomedicine as snake venom antidote in different parts of the globe. This clearly indicates a positive correlation between the ethnic use of medicinal plants and their pharmacological efficacy.

Snakebite is a common occupational hazard faced by the villagers especially the farmers and agricultural labours (Bawaskar, 2004). Antivenom immunotherapy is the most common treatment against snake bite. Conventional antivenins include Equine (horse derived) or Ovine (sheep derived) immunoglobulin F(ab')2 fragments and Fab, generated by pepsin and papain digestion (Paul *et al*., 2011; Gutierrez *et al*., 2011a). Undesirable side effects, inability to prevent already caused damage, occasional ineffectiveness of intravenous application, requirement of time in anti venin development, higher price, limited supply and the necessity of proper storage conditions are among the limitations of conventional anti venin drugs (Paul *et al*., 2011; Meenatchisundaram *et al*., 2008). Lack of medical infrastructure, remoteness of occurrence, wrong treatment by the quacks and ineffectiveness of anti venin due to poor storage cause a number of deaths due to snakebite in rural areas. Correct use and cost effectiveness of these antivenoms are the two major concerns in the low-income countries of the tropics (Gutierrez *et al*., 2011a). Efficacy and safety are among the other important criteria of anti venin (Gutierrez *et al*., 2011b). Development of tetanus has been a problem associated with the use of crude folk medicine (Ehui *et al*., 2007). Investigations on the development of affordable antivenoms for the under privileged counties have been carried out (Williams *et al*., 2011). However, standardization and control of the antivenoms are of utmost importance (Theakston *et al*., 2003).

CONCLUSION

Herbs and herbal products have been used in the remedy of several human ailments. Medicinal plants are being popularized as an exciting aspect of alternative therapy due to less or no side effects, cost effectiveness and lack of development of drug resistance. Snakebite, one of the major causes of mortality in tropical and subtropical countries, is treated with conventional animal based anti venin. However, the rural folks of third world countries apply various medicinal plants in their crude forms or with some additives as antidote to snakebites. Some of these antiophidians have been evaluated pharmacologically for potential anti venin and positive outcome from the experiments has indicated possible therapeutic value of the botanicals. Therefore, herb based antivenin might serve as an alternative treatment against snake venom provided the tests pass through the rigors of clinical trials.

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