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Article

Anti-Snake Venom Properties of Medicinal Plants: A Comprehensive Systematic Review of Literature

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Snakebite is one of the major health issues posing considerable morbidity and mortality. According to an estimate of World Health Organization (WHO) (World health organization, 2021) approximately 5 million people are bitten by several species of snakes resulting in up to 2.5 million envenomation cases annually. The mainstay of treatment for envenomation is intravenous administration of anti-snake venom. Although antivenom neutralizes the systemic effects but it does not relieve the symptoms such as venom-induced hemorrhage, necrosis and nephrotoxicity. Moreover, the use of antivenoms is associated with hypersensitivity reactions including urticaria, anaphylaxis, or serum sickness due to their heterologous property. Furthermore, stringent storage conditions and narrow specificity of antivenoms limit their use in both developed as well as developing countries. In this context, researchers have been searching for natural products and plant extracts to explore their antivenom activity along with anti-myotoxic, anti-hemorrhagic and anti-inflammatory properties. Plant remedies may prove to be an effective alternate for antivenom sera with less adverse events and better tolerability. To the best of our knowledge, this is the first comprehensive review of medicinal plants possessing anti-snake venom activities against certain species of snakes. The current review highlights the investigated plants with their phytochemical analysis to integrate the available information for future research and development of antivenom sera.

Keywords: Snake Bite. Anti-snake venom. Medicinal plants. Poisoning. Venomous.

BACKGROUND

Snakebite is a public health concern and considered one of the major causes of death in Southeast Asia (MeeraBai, 2014). The global incidence of snake bites is estimated to be around 5 million (Ameen *et al.,* 2015), and approximately 70,000 in Central America (Giovannini, Howes, 2017). Of these, nearly 25,000 people die in India while around 10,000 people die in the United States each year (Sanusi *et al*., 2014). Approximately 400,000 patients who survive the snake bites may live with permanent amputations and injuries (Giovannini, Howes, 2017). Black mouthed Mamba, Australian cobra, Saw-scaled viper, King cobra and Coastal Taipan are among the top ten deadliest snakes around the globe. These species belong to the Elapidae and Viperidae families (Félix-Silva *et al*., 2017). Predominant snake species present in the Indo-Pak region are Common cobra, King cobra, Russell's viper, Pit viper, Saw-scaled viper and Sea snakes (Alirol *et al*., 2010).

The course of snake envenomation is different across several snake species. Some snakes sting their prey without inserting the poison (dry bite) while others inject highly toxic venom through modified salivary glands resulting in death of prey. Dry bite snakes are also considered harmful as their dribble may possess *Clostridium tetany* which

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may result in death, if left untreated (Rita *et al.,* 2011). During the process of envenomation, the venom passes from glands to fangs through a duct and finally it reaches to the prey (Félix-Silva *et al*., 2017; Rita *et al*., 2011). The typical signs of snake envenomation are hysteria, which results in an increased heartbeat, emesis, lightheadedness, tachycardia, hypotension, vertigo, sticky and perspiring skin (Gutiérrez, Theakston, Warrell, 2006). Chemically snake venom is comprised of proteins and enzymes, which interact with the physiology and anatomy of prey, thus causing significant harm. The phosphodiesterase and cholinesterase constitute an immense proportion of enzymes present in snake venom. Phosphodiesterase mainly interacts with the prey's cardiac system, resulting in lowering of blood pressure, while cholinesterase makes the prey to lose control over its muscles. Similarly, some snake venoms contain amino acid oxidases which particularly digest the amino acids and stimulate other enzymes (Mitra, Mukherjee, 2014)**.** Phospholipase A2 (PLA2) is the most studied and clinically significant constituent of snake venom. This enzyme is categorized into two groups including I-A and II-A. Venoms of *Naja Naja* and *Daboia russelli* are primarily composed of I-PLA2 and II-PLA2, respectively (Kumar *et al*., 2019; Bhat, Gowda, 1989; Raghavamma, Rao, Rao, 2016).

Monovalent and polyvalent antivenoms are unique types of antidotes for snakebite management (Kumar *et al*., 2019). Considering the cost-effectiveness and accessibility, the use of monovalent antivenoms is more frequent than polyvalent antivenoms. Moreover, the allergic reactions attributed to the antibodies present in polyvalent antivenoms limit their use in clinical practice. Consequently, the utilization of antivenoms in reducing snake bite associated morbidity, disability and mortality have been limited by multiple factors including wide adverse effects profile, stringent storage conditions, specificity issues, risk of immunological reactions and high cost (Félix-Silva *et al*., 2017. The consequence of these shortcomings has been more dramatic in developing countries where locally manufactured anti-venoms does not meet the needs of the population. Therefore, different plant species are being used as alternatives (Makhija, Khamar, 2010; Premendran *et al*., 2011). The researchers have been looking after various medicinal plants and their extracts to explore the possible anti-snake venom activity with maximum safety profile (Félix-Silva *et al*., 2017). There is a dire need to explore alternative sources that can be employed as anti-snake venoms. Various reports and studies have documented the use of herbal antidotes against snake envenomation. Many tribal communities and local inhabitants of various tropical and sub-tropical regions have been using herbal sources for the management of snakebite (Kumar *et al*., 2016; Félix-Silva *et al.,* 2017). The current review aims to underscore the available scientific evidence related to plant use for the treatment of envenomation.

Search Methodology

Selection Criteria for Studies

The current review describes the recent advances in this area in order to provide precise and comprehensive information on anti-ophidic activity of medicinal plants against several snake species. All available information of main botanical families with anti-ophidian activity and their secondary metabolites showing venom neutralizing ability were collected via an electronic search of different scientific sources including Pubmed (https://www.ncbi.nlm.nih.gov/pubmed), Science Direct (https://www.scopus.com/), Google Scholar (https://www.scopus.com/), Scientific Electronic Library Online (SciELO) (http://www.scielo.org/), Cochrane library (https:// www.cochranelibrary.com/), and Web of Science (http://www.webofknowledge.com/). The study database encompassed articles of peer-reviewed journals, books, thesis, dissertations, various patents and supplementary reports covering anti-snake venom properties of medicinal plants from date of inception to Dec 2019. The botanical names of medicinal plants were confirmed in at least 2 botanical databases before citing in this review. The botanical databases included NCBI Taxonomy Browser (https://www.ncbi.nlm.nih.gov/taxonomy), Tropicos (http://www.tropicos.org), Flora of Pakistan (http://www.efloras.org/), The plant list (http://www.theplantlist.org/), Flora do Brasil (http://www.floradobrasil.jbrj.gov.br/) and the Flora of India (http://www.ecoindia.com/).

Search Strategy

Authors opted the following keywords to find the relevant studies:

"Plants", "medicinal plants", "herbal remedies", "herbal alternatives", "traditional medicine", "alternative medicine", 'plants with anti-snake venom potential", "plants having anti-snake venom potential", "plants with anti-ophidic activity", "natural alternatives of anti-snake venoms", "alternative therapy to treat snake bite", "snake bite remedies", "botanical families with anti-ophidic potential", "plant extract with anti-snake venom potential", "investigated plant extract against snake venom", "snake toxin inhibitors", "snake venom inhibitors", "venom neutralizing potential of plants", "phospholipase A2 inhibitors", "anti-ophidics", "anti-ophidian potential", "anti-toxins", "anti-hemorrhagic potential", "Borthop", "Cobra venom", "Russel viper", "daboia", "pit viper". These terms were either used alone or in combination by using Boolean operators ("and", "or", "not").

The studies related to the ethnobotanical survey of plants with anti-ophidic activity and the phytochemical analysis of anti-ophidic plants were selected and subjected to critical review. Furthermore, the papers analyzing the efficacy of various phytoconstituents against specific snake venom species were also included. With the information assembled through these studies, the actual scenario of the folklore use of plants and their pharmacologically investigated phytoconstituents against snake venom were pointed out. Major botanical families having established anti-snake venom activity and their common mode of use employed by traditional healers were described. The purpose of the studies selected for this review was to give an overview of plants not only with established traditional anti-ophidic activity in literature but also with investigated phytoconstituents of various plants against specific snake species.

Traditionally Used Plants for Snakebite Management

Most of the medicinal plants mitigate the symptoms of envenomation while some of them show their action by triggering the immune system. Currently, many plant species, in whole or in parts, are being used against snake poisoning, such as *Abutilon indicum* leaf paste, *Acorus calamus* root paste, *Adhota vesica* bark decoction, *Amaranthus viridis* root paste, *Citrus limon* paste, *Curcuma longa* paste, *Dalbergia melanoxylon* decoction*, Eucalyptus globules* juice*, Helianthus annuus* oil, *Mimosa pudica* rice water paste, *Nerium oleander* paste, *Nicotiana tobaccum* decoction, *Piper nigrum* paste with ghee, *Phyllanthus emblica juice*, *Rauvolfia serpentina* paste, *Solanum torvum* paste, *Strychnos nux vomica* paste, *Thymus vulgaris juice*, *Wedelia calendulae* juice and *Woodfordia fruticosa* paste (Kumar *et al*., 2016; Vásquez *et al*., 2015; Makhija, Khamar, 2010; Rita *et al*., 2011; Selvanayagam *et al*., 1995). According to a study elaborating the cross-cultural comparison of medicinal floras for snake venom conducted by Molander *et al.* (2012), the most prominent botanical families with marked anti-ophidic property included *Asteraceae, Apocynaceae, Araceae, Fabaceae, Euphorbiaceae, Lamiaceae, Malvaceae, Rubiaceae and Zingeberaceae* (Félix-Silva *et al.,* 2017).

Traditionally, several plant species are used to detoxify the snake venoms through different ways including topical application on affected areas, chewing leaves or bark and drinking or injecting the plant extracts. However, presently the traditional healers are merely utilizing pure plant solutions to heal snake envenomation. Root and leaf extracts of *Abrus precatorius* and *Azadirachta indica* are specifically used against krait and viper bites respectively. Rhizomes of certain curcuma species are beneficial against the Thai cobra neurotoxin. Stem and bark extracts of *Brownea rosademonte* and *Tabebuia rosea* possess antihemorrhagic property against *Bothrops atrox* venom. Similarly, decoctions of *Alangium salvifolium, Argemone mexicana, Dalbergia melanoxylon, Hemidesmus indicus, Sansevieria trifasciata* and *Syzygium cumini* can be taken orally to neutralize the snake venom. However, various plants simply require a topical application on the affected areas. The paste from *Achyranthes aspera, Acorus calamus, Allium cepa, Citrus limon, Ehretia buxifolia, Gloriosa superba, Madhuca longifoila, Tapirira guianensis, Terminalia arjuna* is applied gently over the affected area for 2 to 7 days following the envenomation. A paste of *Calotropis gigantean* roots, mixed with ghee (saturated oil) is ingested to fight against the snake venom. Whereas, the oil from *Tapirira guianensis* is applied over the skin in an ointment form to treat the affected area. Despite the isolation of certain phytochemicals from plants, their approval requires several preliminary concerns of safety and efficacy (Butt *et al*., 2015; Dey, De, 2012; Félix-Silva *et al*., 2017; Makhija, Khamar, 2010; Sajon, Sana, Rana, 2017; Samy *et al*., 2008). Extensive efforts have been made to verify the anti-ophidic potential of traditionally used plants. Existing literature underscores scientific evidence of these plants against various snake species (Harder *et al*., 2017; Alam , Gomes, 2003). Table I summarizes some important plant species traditionally used for snakebite management.

TABLE I - Traditionally used plants for Snakebite Management

Plant specie	Family	Common name	Part used	Direction of use	Administration	References
Abrus precatorius	Leguminosae	Kundumani	Roots	Unknown	Orally for 5 days	(Makhija, Khamar, 2010)
Abutilon indicum	Malvaceae	Atibala	Leaf	Leaf juice Mixed with jiggery Fruits	Oral (2days)	(Uawonggul *et al*., 2006)
Acacia leucophloea	Mimosaceae	White bark	Bark	Paste	External (1 Week)	(Samy *et al*., 2008)
Achillea millefolium	Asteraceae	Mountain yarrow	Whole plant	Paste	Oral (6 days)	(Makhija, Khamar, 2010)
Achyranthes aspera	Amaranthaceae	Nayuruvi	Leaf	Paste	External (3Weeks)	(Butt *et al*., 2015; Makhija, Khamar, 2010)
Acorus calamus	Araceae	Vasambo	Rhizome	Paste	External (7 days)	(Verma, Singh, 2008)
Aegle marmelos	Rutaceae	Vilvam	Root bark	Aqueous Decoction	Oral (2 Weeks)	(Panghal *et al*., 2010)
Aerva lanata	Amaranthaceae	Poolapo	Rhizome	Unknown	Oral (11 days)	(Selvanayagam *et al*., 1995)
Alangium salvifolium	Alangiaceae	Alangi	Root bark	Decoction	Oral (twice a day up to 4 days)	(Makhija, Khamar, 2010: Alagesaboopathi, 2013)
Allium cepa	Liliaceae	Venkayam	Skin bulb	Paste	External application (5 days)	(Butt *et al*., 2015; Samy *et al*., 2008)
Amaranthus dubius	Amaranthaceae	Gusanito	Leaves, root and seed	Ointment	Applied externally	(Félix-Silva *et al*., 2017)
Andrographis paniculata	Acanthaceae	Periyananghai	Whole plant	Decoction, Paste	External (5–14 days)	(Uawonggul *et al*., 2006)
Argemone mexicana	Papaveraceae	Barahmathandu	Leaf, Seed	Decoction	Oral (7 days)	(Samy *et al*., 2008; Verma, Singh, 2008)
Aristolochia indica	(Aristolochiaceae)	Birthwort	Whole plant	Root extract	Paste External (1 Week)	(Meenatchisundaram, Parameswari, Michael, 2009)
Azadirachta indica	Meliaceae	Neem, Wimpu	Flower	Decoction	Oral (7 days)	(Dey, De, 2012)

TABLE I - Traditionally used plants for Snakebite Management

Plant specie	Family	Common name	Part used	Direction of use	Administration	References
Calotropis gigantea	Asclipiadaceae	Madar, Crown flower, Milkweed	Latex, Leaf, Root	Fresh latex Paste with ghee	Oral (3–7 days) and externally	(Félix-Silva *et al*., 2017; Yogi, Gupta, Mishra, 2016; Dey, De, 2012)
Cassia alata	Caesalpiniaceae	Senna	Leaf	Paste	Oral (21 days)	(Rahmatullah *et al*., 2009; Samy *et al.,* 2008)
Cassia tora	Caesalpiniaceae	Tagarai	Leaf	Decoction	Topical (14 days)	(Mors *et al.,* 1989; Samy *et al.,* 2008)
Citrus limon	Rutaceae	Elumichai	Ripe skin	Paste	External (3 days)	(Gomes *et al*., 2010; Samy *et al*., 2008)
Curcuma longa	Zingiberaceae	Haldi	Whole plant	Paste	Paste is taken orally and applied	(Kumar *et al*, 2016)
Dalbergia melanoxylon	Fabaceae	Veelipruthi	Stem bark	Decoction	Oral (6 days)	(Kala, 2009; Samy *et al*., 2008)
Dracontium spruceanum	Araceae	Chupa, Chupadera	Roots, Leaves	Direct heating decoction	Externally	(Félix-Silva *et al*., 2017)
Dracontium spruceanum	Araceae	candelillachupadera	Rhizome, Stem, Leave	Extract, Poultice	Internally, externally	(Giovannini, Howes, 2017)
Ehretia buxifolia	Ehretiaceae	Thelchedi	Root	Paste	External (7 days)	(Samy *et al*., 2008; Selvanayagam *et al*., 1996)
Feronica limonia	Rutaceae	Elephant apple	Root	Juice	Oral (3 days)	(Makhija, Khamar, 2010)
Gloriosa superba	Liliaceae	Kalappaih kilangu	Tuber	Paste	External (2–5 days)	(Jana, Shekhawat, 2011; Minu *et al.,* 2012)
Gymnema sylvestre	Asclepiadaceae	Gurmarbuti	Root	Tincture	Oral (4 days)	(Kini, Gowda, 1982; Sajon, Sana, Rana, 2017; Samy *et al*., 2008)
Hemidesmus indicus	Asclepiadaceae	Anantamul	Root	Decoction	Oral (7 days)	(Dey, De, 2012; Uawonggul *et al.,* 2006)
Madhuca longifoila	Sapotaceae	Saathikkai	Nut	Paste	External (2–3 days)	(Akshatha, Murthy, Lakshmidevi, 2013; Minu *et al.,* 2012)
Mimosa pudica	Leguminosae	Touch-me-not, Chui mui	Creeper Root	Paste	Paste is mixed with raw rice water and given orally	(Krishna *et al*., 2014; Alam *et al*., 2003; Kumar *et al*, 2016)
Momordica charantia	Curcubitaceae	Karela	Leaf, Stem, Fruit	Extract	Oral	(Asad *et al*., 2014; Giovannini, Howes, 2017)
Moringa oleifera	Moringaceae	Murunghai	Bark, Root	Tincture	External (3 days)	(Makhija, Khamar, 2010; Minu *et al*., 2012)
Morus alba	Moreaceae	Mulberry llai	Leaf	Juice	Oral (3 Weeks)	(Dey, De, 2012; Uawonggul *et al.,* 2006)

TABLE I - Traditionally used plants for Snakebite Management

Plant specie	Family	Common name	Part used	Direction of use	Administration	References
Ocimum sanctum	Lamiaceae	Tulasi	Leaf	Juice	Oral (8 days)	(Panghal *et al.,* 2010)
Ophiorrhiza mungos	Rubiaceae	Napali	Root	Juice	Oral (Twice a day for 6 days)	(Krishnan *et al.,* 2014; Makhija, Khamar, 2010; Samy *et al.,* 2008)
Rauvolfia serpentine	Apocynaceae	Sarpgandha	Root	Unknown	External (10 days)	(Makhija, Khamar, 2010; Samy *et al.,* 2008)
Sansevieria trifasciata	Asparagaceae	Lirio de tigre	Ariel parts	Decoction	External	(Félix-Silva *et al*., 2017)
Sapindus emargiatus	Sapindaceae	Puvam kottai	Bark	Paste	Bark Paste	(Minu *et al*., 2012; Penchalapratap *et al*., 2010)
Strychnos nux-vomica	Loganiaceae	Visakkotai	Bark	Paste	External (12 days)	(Chatterjee, Chakravarty, Gomes, 2004; Makhija, Khamar, 2010; Samy *et al.,* 2008)
Syzygium cumini	Myrtaceae	Naeralae	Stem bark	Decoction	Oral (14 days)	(Makhija, Khamar, 2010; Samy *et al.,* 2008)
Tapirira guianensis	Anacardiaceae	Fresmo	Oil	Ointment	Applied externally	(Félix-Silva *et al*., 2017)
Terminalia arjuna	Combretaceae	Marutham	Bark	Paste	External (5 days)	(Makhija, Khamar, 2010; Minu *et al.,* 2012)
Trichodema zeylanicum	Boraginaceae	Camel bush	Root	Aqueous extract	Oral and External (3 days)	(Asad *et al.,* 2011)
Wedelia calendulae	Asteraceae	Karisilangkanni	Leaf	Juice	Internally (14 days)	(Makhija, Khamar, 2010; Girish, Kemparaju, 2011; Samy *et al.,* 2008)

Investigated Plant Extracts Activity as Anti-Snake Venom

Various researchers have been looking for the development of snake venom antagonists from several botanical sources. Traditional healers primarily rely on plant extracts to treat snakebite envenomation, particularly in tropical regions where plentiful herbal sources are available (Daduang *et al.,* 2005) Numerous studies have reported various botanical families (*Apocynaceae, Fabaceae, Euphorbiaceae, Malvaceae, Rubiaceae* and *Zingiberaceae*) with potential activities against snake envenomation. A growing body of evidence is available to demonstrate the potential benefits of these plants against snake envenomation. A study conducted by Shirwaikar *et al.,* (2004) reported the potent anti-ophidian activity of ethanolic extracts of *Acalypha indica* both in-vitro and in-vivo. An extension of this report revealed even greater anti-ophidian activity of *Acalypha indica*'s acetone extract (Rajendran *et al.,* 2010). The major concern for the development of anti-sake venom drugs from a plant source is to investigate the exact phytoconstituent responsible for particular anti-snake venom activity. On the other hand, anti-ophidian activity is only tested in mice models and very few clinical studies have been conducted so far to establish the anti-ophidian claim of investigated plant extracts. Likewise, anti-snake venom activity of ethanolic extract of *Piper longa* and piperine against Russell's viper venom was demonstrated by P.A. Shenoy *et al.,* (2013) through embryonated fertile chicken eggs, mice and rats model. Extensive research is needed to assess the efficacy, stability and compatibility of isolated phytoconstituent with anti-ophidian activity in various pharmaceutical formulations. Available studies suggested the monovalent nature of plant extracts against specific snake venom species. In order to find out an economical and effective antivenom from plant sources, a polyvalent antivenom would be more practical and preferred over monovalent anti-snake venoms (Rojnuckarin, 2013). Premendran *et al.,* (2011) compared the anti-snake venom potential of *Andrographis paniculata* with polyvalent anti-snake venom. The observations recorded a high potential of polyvalent anti-snake venom in inhibiting Cobra's venom than the alcoholic extract of *A. Paniculata*. Table II illustrates laboratory investigations evaluating various plants against specific snake species.

TABLE II - Investigated Medicinal Plans against various Snake Species

Plant species	Family	Part used	Phytoconstituents	Extract Solution	Snake Specie	Reference
Acalypha indica	Euphorbiaceae	Leaves	Flavonoids	Methanol	Russell's viper	(Goswami, Samant, Srivastava, 2014; Samy *et al*., 2008; Shirwaikar *et al,* 2004, Janardhan *et al*., 2014)
Andrographis paniculata	Acanthaceae	Herb	Terpenes Imam	Methanol	Naja naja venom	(Rao *et al*., 2004; Samy *et al.,* 2008; Gupta, Peshin, 2012; Mitra, Mukherjee, 2012; Premendran *et al*., 2011, Nisha, Sreekumar, Biju, 2016)
Aristolochia sp.	Aristolochiaceae	Roots	Aristolochic acid	Methanol	Daboia russelli and Echis carinatus	(Tsai, Yang, Chang, 1980)
Bredemeyera floribunda	Polygalaceae	Roots	Bredemeyeroside D and B, triterpenoid saponins	Methanol, Aqueous	Bothrops jararacussu	(Pereira *et al*., 1996; Alves *et al*., 2019),
Brongniartia podalyriaides	Leguminosae	Roots	Edunol a prenylated pterocarpan	Petrolmethylene chloride	Bothrops atros	(Reyes-Chilpa *et al.,* 1994; Makhija, Khamar, 2010)
Casearia sylvestris	Salicaceae	Bark, leaves	Ellagic acid	Aqueous	Bothrops jaracaca	(Gupta, Peshin, 2012)
Combretum leprosum	Combretaceae	Roots	Triterpene arjunolic acid	Ethanolic extract	Bothrops jararacussus	(Fernandes *et al*., 2014)

TABLE II - Investigated Medicinal Plans against various Snake Species

Plant species	Family	Part used	Phytoconstituents	Extract Solution	Snake Specie	Reference
Cordia macleodii	Ehretiacae	Bark	Flavonoids	Ethanolic extract	Naja naja	(Nayak, Kalidass, 2016; Soni, Bodakhe, 2014)
Crinum jagus	Amaryllidaceae	Bulb	Alkaloids	Methanol	Echis ocellatus, Naja nigricollis.and Bitis arietans	(Mors *et al*., 1989; Ode, Asuzu, 2006)
Curcuma longa	Zingiberaceae	Rhizome	Polyphenolic curcuminoid; curcumin	Aqueous	Naja sp,	(Chethankumar, Srinivas, 2008; Nisha, Sreekumar, Biju, 2016; Ferreira *et al*.,1992)
Echinacea purpurea	Asteraceae	Roots	Echinacoside, cichoric acid, ketoalkenes, alkyl amides and polysaccharides	Aqueous	Bothrops asper	(Chaves *et al*., 2007; Rita *et al*., 2010)
Eclipta prostrata	Asteraceae	Roots	Wedelolactone, sitosterol, stigmasterol	Butanol	Malayan pit viper	(Dey, De, 2012; Mors *et al*., 1989; Janardhan *et al*., 2014; Bhattacharjee, Bhattacharyya, 2013)
Emblica officinalis	Euphorbiaceae	Roots	Phthalate	Methanol	Naja kaouthia	(Alam, Gomes, 2003; Chatterjee, Chakravarty, Gomes, 2004)
Glycyrrhiza glabra	Leguminosae	Roots	Triterpenoid saponins, glycyrrhizin	Aqueous	Bothrops jararaca	(Abe *et al.,* 1998; Assafim *et al*., 2006),
Harpalyce brasiliana	Fabaceae	Roots	Eudanol	Methanol	Bothrops jaracaca, Naja naja	(da Silva *et al*., 2004; Gupta, Peshin, 2012; Ximenes *et al*., 2012)
Hemidesmus indicus	Asclepiadaceae	Roots	Hydroxy-4-methoxy benzoic acid, Lupeol acetate	Methanol	Daboia russelli	(Chatterjee, Chakravarty, Gomes, 2006; Gomes *et al*., 2007; Meenatchisundaram, 2008; Janardhan *et al*., 2014)
Musa parad	Musaceae	Stem	Saponins	Juice	Bothrops jararacussu	(Borges *et al*., 2005; Imam, Akter, 2011; Samy *et al*., 2008)
Pergularia daemia	Asclepiadaceae	Stem Bark	B-sitosterol	Aqueous	Naja Naja	(Raghavamm, Rao, Rao*,* 2016)

TABLE II - Investigated Medicinal Plans against various Snake Species

Plant species	Family	Part used	Phytoconstituents	Extract Solution	Snake Specie	Reference
Periandra mediterranea	Leguminosae	Roots	Saponins	Aqueous	Bothrops jaracaca	(Houghton, Osibogun, Bansal, 1992; Makhija, Khamar, 2010)
Schuanniophyton magnificum	Rubiaceae	Root bark	Chromone alkaloidal glycoside schumanniofoside	Aqueous	Naja melanoleuca, Naja kaouthia	(Dey, De, 2012; Houghton, Osibogun, Bansal, 1992; Makhija, Khamar, 2010)
Symplocos racemosa	Symplocaceae	Bark	Salireposide and benzoylsalireposide, phenolic glycosides	Aqueous	-	(Ahmad *et al*., 2003; Ahmad *et al*., 2004; Bhusnar, Nagore, Nipanikar, 2014)
Tabernaemontana catharinensis	Apocyanacea	Root	12-methoxy-4-methylvoachalotine	Aqueous	Crotalus durissus terrificus	Batina *et al*., 2000; Singh *et al*., 2017)
Vitis vinefera	Vitaceae	Seed	P-Hydroxybenzoic acid	Methanolic	Echis carinatus	(Gupta, Peshin, 2012; Mahadeswaraswamy *et al*., 2008; Mahadeswaraswamy *et al*., 2008)
Cordia verbenacea	bragenaceae	Leave	Rosmarinic acid	Methanol	Bothrops jararacussu	(Pereira *et al*., 2009; Dey, De, 2012)
Pluchea indica	Asteraceae	Root	Stigma sterol and beta sterol	Methanol	Daboia russelii and N. kaouthia	(Gomes *et al*., 2007)
Plathymenia reticulata	Fabaceae	Bark	Diterpenes, vinhaticyl acetate and methyl vinhaticoate	Aqueous	Bothrops atrox	(de Moura *et al*., 2016)

Phytoconstituents of Traditional Plants Used as Anti-Snake Venoms

The phytochemical analysis of various plants has revealed that phenols, alkaloids, triterpenoids and steroids possess promising anti-ophidic activity against snake venom. Several plants including *Aegle marmelos, Centipeda minima, Aloe vera, Phyllanthus niruri, Alstonia scholaris, Phyllanthus emblica, Elephentopus scaber* contain pentacyclic triterpenes which provide protection against snake venoms (Samy *et al*., 2008). Similarly, *Pentace burmanica, Pithecellobium dulce, Areca catechu* and *Quercus infectoria* comprise of polyphenols that neutralize the *Naja kaouthia* (NK) venom (Pithayanukul *et al*., 2005).

Over the past few decades, several studies have pointed out the efficacy of various phytoconstituents present in crude extracts of plants (e.g. *Eclipta prostrate*) against phospholipase A2 (PLA2s) enzymes (Marcussi *et al*., 2007; Soares *et al*., 2014)**.** In addition to PLA2s inhibition, the phytoconstituents such as terpenes, flavonoids and phenols exhibit protein binding and enzyme inhibition characteritics (Selvanayagam *et al.,* 1996). Myricetin, quercetin and amenthoflavone are the famous flavonoids with antihemorrhagic activity. Among these flavonoids, quercetin was reported to be the most potent lipoxygenase inhibitor (Nishijima *et al.,* 2009). *Diospyrus kaki* possesses antihemorrhagic property due to the presence of tannins (Martz, 1992). The treatment with concentrates of *Andrographis paniculate* and *Diodia scandens* is reported to extend the survival duration of the victim (Nazimudeen *et al.,* 1978). Edunol, isolated from *Harpalyce brasiliana,* is reported to possess anti-proteolytic activity. Furthermore, *Hemidesmus indicus* is utilized to inhibit PLA2, owing to the presence of lupeol acetate in its roots. (Chatterjee, Chakravarty, Gomes, 2006). Table III outlines the investigated phytoconstituents of the plants employed as alternatives to anti-snake venoms.

TABLE III - Phytoconstituents of traditional plants with antivenom activity

Plant Species	Isolated phytoconstituents	Reference
Aristolochia sp	Aristolochic acid	(Makhija, Khamar, 2010)
Azadirachta indica	Aiplai (*a. Indica* pla2 inhibitor)	(Mukherjee, Doley, Saikia, 2008)
Bellucia dichotoma	Condensed tannins	(de Moura *et al.,*2017)
Betula alba	Betulin and betulin acid	(Bernard *et al.,* 2001)
Bridelia ndellensi	Quinovic acid glycosides	(Mostafa *et al.,* 2006)
Camellia sinensis	Theaflavin and Epigallocatechin	(Pithayanukul, Leanpolchareanchai, Bavovada, 2010; Rosa *et al*., 2010)
Canavalia ensiformis	Concanavalin a (con-a)	(Dhananjaya, D’souza, 2010)
Cardiospermum halicacabum	Berberine	(Sebastin *et al*., 2013)
Casearia sylvestris	Ellagic acid from	(Gupta, Peshin, 2012)
Cordia verbenacea	Edunol *brongniartia podalyrloides* anti-lethal activity rosmarinic acid	(Soares *et al*., 2014; Ticli *et al*., 2005)
Cyclea peltata	Stigmasterol, phytosterol	(Sivaraman *et al.,*2017)
Eclipta prostrata	Wedelolactone	(Marcussi *et al*., 2007)
Harpalyce brasiliana,	Edunol, a pterocarpan	(da Silva *et al*., 2004; Samy, Gopalakrishnakone, Chow*,* 2012)
Jatropha gossypiifolia	Flavonoids	(Felix-Silva *et al.,*2017)
Kalanchoe pinnata	Patuletin, quercetin, kaempferol	(Fernandes *et al.,* 2016)
Mandevilla velutina	Steroids	(Mahanta, Mukherjee, 2001; Makhija, Khamar, 2010)
Mangifera indica	Pentagalloyl glucopyranose	(Leanpolchareanchai *et al*., 2009; Rahmatullah *et al*., 2012)
Mimosa pudica	B-3-(3-hydroxy-4-oxopyridyl) a-amino propionic acid, the mimosine	(Mahadeswaraswamy *et al*., 2011)
Piper peltatum	4-nerolidylcatechol	(Kobayashi *et al*., 2005)
Piper umbellatum	4-nerolidylcatechol	(Makhija, Khamar, 2010; Núñez *et al.,* 2005)
Strychnos nux vomica	Amide	(Chatterjee, Chakravarty, Gomes, 2004)

TABLE III - Phytoconstituents of traditional plants with antivenom activity

Plant Species	Isolated phytoconstituents	Reference
Tragia involucrata	2, 4 dimethyl hexane, 2 methyl nonane, 2, 6 dimethyl heptane	(Samy, Gopalakrishnakone, Chow, 2012)
Vitex negundo	Tris (2,4-di-tert-butylphenyl) phosphate (tdtbpp)	(Alam, Gomes, 2003; Vinuchakkaravarthy *et al.,* 2011)
Withania somnifera	Glycoprotein	(Marcussi *et al*., 2007)
Baccharis trimera	Betulinic acid; 4-nerolidylcatechol; clerodane; betulin	(Sebastin *et al.,* 2013)
Tabernamontana catharinensis	12-methoxy-4- methylvoachalotine alkaloid	(Batina *et al*., 2000; Sebastin *et al*., 2013)
Harpalyce brasiliana	Edunol	(da Silva *et al*., 2004; Sebastin *et al.,* 2013)

Identification of Venoms and Toxins

Early identification of venom involved in envenomation is of great importance to choose the appropriate therapeutic measures. Since many snake bites share similar clinical manifestations, it is quite difficult and sometimes impractical to rule out the snake species involved in envenomation. Bioassays, immune diffusion, immune electrophoresis, immunofluorescence, haemagglutination, radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) are few analytical methods that are used to detect venom involved in the poisoning. Hybridoma technology and affinity chromatography have also been used for diagnostic purposes (Bawaskar, 2004). Recently, optical immunoassay (OIA), venom/antibody micro-array assay, polymerase chain reaction (PCR) and surface plasmon resonance (SPR) are also utilized for the venom detection (Choudhury *et al.,* 2018).

Limitations of Anti-Snake Venoms from Botanical Origin

Kingdom Plantae provides numerous alternatives for anti-snake venoms. Despite the immense reliability on plants for the snakebite treatment due to their safety, efficacy, cost-effectiveness and cultural preferences, the herbal treatment of snake envenomation is least appreciated in modern medicine. Since a limited number of studies have evaluated the pharmacologically active phytoconstituents of plants possessing anti-ophidic activity, validation of herbal remedies is still questionable and requires further attention of researchers (Gupta, Peshin, 2012). Only specific species of plants are reported to be beneficial against snakebites in traditional healing. Similarly, the amount of snake venom is also an important issue. Furthermore, there is a lack of human evidence as most of the plant extracts are being tested on animal models.

CONCLUSION

The low cost, easy accessibility, fewer stability issues and broad-spectrum anti-ophidic activity against various venoms make plants as favorable choice against snake envenomations. It is pertinent to mention that antivenoms are not readily available in most of the cases of snakebite, particulary in underdeveloped regions. In such instances, herbal therapeutics seems to be a viable alternative. Findings of the current review conclude that plants are extremely rich source of active phytoconstituents with an established anti-ophidic potential against one or more snake venoms. Of these, triterpenes, aristocholic acid, cinnamic acid, benzoic and chlorogenic acid derivatives, steroids, flavonoids, polysaccharides and polyphenols are significant in snakebite management. However, currently available studies have only established the monovalent nature of various plant extracts against specific snake venoms. Since snake species are hardly identifiable during the clinical practice, the polyvalent anti-venom nature of phytoconstituents with relatively fewer side effects should be sought. Despite the growing body of evidence on promising anti-ophidic potential of various medicinal plants, no plant based anti-snake venom is commercially available. These findings necessitate the dire need of thorough investigations and extensive research at biochemical and molecular levels. Appropriate selection of plant species with optimum potential is of utmost importance and can be carried out through scientific validation of conventional therapies. Moreover, standardization of the active components along with safety and toxicity profile is mandatory. The current review illustrates the dearth of investigations evaluating the anti-ophidic potential of plants in human beings. Conclusively, the information presented in the current review delivers an updated insight of medicinal plants possessing anti-ophidic activity based on their traditional use in the literature as well as scientific evidence on their neutralizing potential against various vemons. It gives a perception for future research and propose validation of medicinal plants as anti-ophidic agents which can be employed as a tool to design potent inhibitors and/or herbal medicines against snake venoms.

CONFLICTS OF INTEREST

None

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None

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