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Trabalho de Conclusão de Curso de Farmácia

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Iara Sofia Gerhrke Strauch

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Prof. Dr. Marcelo Dutra Arbo

Orientador

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Apresentação

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PLANTS USED IN THE TREATMENT OF SNAKEBITES IN BRAZIL

STRAUCH, I.S.G.; ARBO, M.D.

Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brasil. Av. Ipiranga, 2752 - Azenha, Porto Alegre - RS, CEP 90610-000.

Abstract

Snakebite envenoming is a potentially fatal disease categorized as a neglected public health issue for not receiving the attention it deserves from national and international health authorities. The people most affected by this problem usually live in poor rural communities where medical resources are often sparse and, in some instances, there is even a scarcity of antivenom, which is the only specific treatment. Therefore, there is a need for a search and evaluation of new agents with effective anti-ophidian activity. The aim of this study was to review the scientific bibliography and to compile a list of plant species used in the treatment of snakebites in Brazil caused by the four genera of snakes considered venomous and therefore of medical importance in the country: *Crotalus*, *Bothrops*, *Lachesis* and *Micrurus*. The research was conducted in the databases "Pubmed", "Scielo" and "Google Scholar", using the term "plant snakebites and Brazil", as well as combinations of other keywords, its corresponding terms in portuguese and spanish, and the genera of snakes with clinical relevance in Brazil. In this review, there were found 94 articles that tested determined antiophidic properties of one or more plant species. A total of 104 plant species were reported, belonging to 51 different families. Only eleven species are reported at least three times, other eleven are reported twice and the other 82 plant species are each reported in just one study. The most cited plant species were *Casearia sylvestris* Sw., *Eclipta prostrata* (L.) L., *Mikania glomerata* Spreng., *Schizolobium parahyba* (Vell.) S.F.Blake, *Curcuma longa* L., *Tabernaemontana catharinensis* A.DC., *Kalanchoe laciniata* (L.) DC., *Jatropha gossypiifolia* L., *Marsypianthes chamaedrys* (Vahl) Kuntze, *Bellucia dichotoma* Cogn., and *Renealmia alpinia* (Rottb.) Maas. Further studies on the chemistry and pharmacology of traditionally used plant species will help understanding the role that snakebite herbal remedies can have within local medical health systems and may be useful in the development of alternative or complementary treatments to reduce the number of severe disabilities and deaths.

Keywords: antivenom, snakebite, folk medicine, plant extract, anti-ophidian

1. Introduction

Snakebite envenoming is a potentially fatal disease resulting from the injection of a toxic secretion, the venom, by a venomous snake into the victim through a bite, usually under accidental circumstances. It is estimated that more than 5 million people worldwide are bitten by snakes every year, resulting in about 2.5 million envenomations (development of clinical illness), half of whom request medical care, and probably more than 100,000 individuals suffer from severe sequelae, such as amputations. The consequent mortality rate could range from about 94,000 to 125,000 death per year[1,2].

Despite this numbers, snakebite envenoming is appropriately categorized as a neglected public health issue for not receiving the attention it deserves from national and international health authorities[2,3]. The people most affected by this problem usually live in poor rural communities where medical resources are often sparse and in some instances there is even a scarcity of antivenom, which is the only specific treatment. The impact of these health issues, although dramatic and economically significant, does not appear as a priority in the design of national public health programs[3].

According to data obtained from the Sistema Nacional de Informações Tóxico-Farmacológicas (SINITOX), there were 3,322 cases of intoxication by snakes in Brazil at the year 2016, resulting in 22 deaths (North region was not included in the data)[4]. However, in the same period of time, the Sistema de Informação de Agravos de Notificação (SINAN) registered a total of 26,365 accidents with snakes in the country, mostly of them in the North and Northeast regions[5].

In Brazil, there is a vast diversity of snake species, among which only two families and four genera are known to contain snakes considered venomous and therefore of medical importance: the *Viperidae* family, which includes the genera *Crotalus* (cascavel), *Bothrops* (jararaca) and *Lachesis* (surucucu) and the *Elapidae* family, to which belongs the genus *Micrurus* (coral-verdadeira)[6]. Snake venom is composed of a mixture of toxic peptides and enzymes with a wide range of pharmacological activities[7]. Some toxins in venom cause local tissue damage, often resulting in permanent sequelae, whereas others induce systemic effects[8]. Venoms from snakes of the family *Viperidae* cause local effects and systemic manifestations associated with bleeding, coagulopathies and hypovolaemic shock. Venoms from snakes of the

family *Elapidae* mostly induce neurotoxic manifestations, such as neuromuscular paralysis[8].

The clinical management of snake bite envenoming is centered on the intravenous administration of antivenom, together with a series of auxiliary interventions that include ventilatory support for neurotoxic envenoming, fluid replacement for hypovolaemic shock, dialysis for acute renal failure, tetanus prophylaxis and antibiotics for local wound infection and surgical debridement of necrotic tissue, followed by rehabilitation to restore full function in the bitten limb[3].

Despite being effective against systemic effects, the conventional antisera have no efficiency in reversing local damage. Besides that, heterologous serum can cause several adverse reactions to the snakebite victims[9]. Therefore, there is a need for a search and evaluation of new agents with effective anti-ophidian activity in order to develop alternative or complementary treatments, aiming to improve health care quality, and consequently to reduce the number of severe disabilities and deaths. The aim of this study was to review the scientific bibliography and to compile a list of plant species used in the treatment of snakebites in Brazil. It is beyond the scope of this review to extensively discuss the pharmacological activities for all the recorded species. However, where there is evidence of phytochemical constituents that might be responsible for the antiophidic activity, these are discussed for the most frequently reported species and/or genera.

2. Materials and Methods

The bibliographic research was conducted in the databases “Pubmed”, “Scielo” and “Google Scholar”, using the term “plant snakebites and Brazil”, as well as combinations of keywords such as "antivenom", "venomous snakes", "antiophidic", “antidote”, “plant”, “snake”, “ethnopharmacological”, “ethnobotanical”, “folk medicine”, “ethnomedicine”, “plant treatment”, its corresponding terms in portuguese and spanish, and the genera of snakes with clinical relevance in Brazil: “*Bothrops*”, “*Crotalus*”, “*Micrurus*” and “*Lachesis*”. Whereas the genus *Bothrops* was recently reorganized in other genera (*Bothriopsis*, *Bothrocophias*, *Bothropoides* e *Rhinocerophis*) and the genus *Croatulus* was renamed “*Caudisona”*, these new terms were also utilized in the search. The valid name of plant species and authors was confirmed using the

database The Plant List. The research was conducted in the period of february to june of 2019.

3. Results and discussion

In almost all parts of the world, where venomous snakes occur, numerous plant species are used as folk medicine to treat snakebites. Generally, an aqueous, methanol or ethanol extract is prepared out of the plant parts. Topical application of the plant or its sap onto the bitten area, chewing leaves or barks or drinking plant extracts or decoctions or injecting the extracts are some procedures intended to counteract snake venom activity[10].

The *Bothrops* genus comprises about 30 species distributed throughout all the national territory. These snakes popularly known as "jararaca" inhabit mainly rural areas and peripheries of large cities. Bothropic accident corresponds to the ophidian accident of major epidemiological importance in the country, since it is responsible for about 90% of the envenomations. The venom from these snakes is known to cause clinical manifestations related to proteolytic, coagulant and hemorrhagic actions. The proteolytic action is responsible for the local lesions at the bite site, such as edema and necrosis and is due to activation of proteases, hyaluronidases, and phospholipases, as well as to release of inflammatory response mediators. Haemorrhagic changes may be local or systemic, and are caused by activation of enzymes that provoke lesions in the membrane of the capillaries, associated with thrombocytopenia and coagulation disorders[6].

The *Crotalus* genus groups multiple subspecies belonging to the specie *Crotalus durissus* and are popularly known as "cascavel". They are found in open fields and in dry, sandy and stony areas. These snakes do not usually attack, but when excited, they announce their presence by the characteristic noise of the rattle. This genus is responsible for about 7.7% of ophidian accidents registered in Brazil, and in some regions it represents up to 30% of the accidents. It also presents the highest lethality due to the frequency that the symptoms evolve to acute renal failure. Crotalic venom has three main actions: neurotoxic, myotoxic and coagulant. It is constituted of crotoxin, a neurotoxin that inhibits the release of acetylcholine and causes neuromuscular blockade, leading to motor paralysis. The venom also produces lesions on skeletal muscle fibers (rhabdomyolysis), with release of enzymes and myoglobin to the serum and posterior

excretion in urine. The fraction responsible for the myotoxic action is still unknown. Haemorrhagic manifestations when present, are discret[6].

The *Lachesis* genus comprises the species *Lachesis muta* with two subspecies. These snakes, popularly known as "surucucu", are the largest venomous snakes in America, reaching up to 3.5 m. There are only a few case reports of accidents with *Lachesis*, probably because they inhabit forest areas, such as the Amazon and the Atlantic Forest, where the population density is low and notification systems are not so effective. Therefore, information available about this type of envenomation is scarce. Proteolytic, coagulant, haemorrhagic and neurotoxic activities are described, and clinical manifestations are similar to bothropic accidents[6]. These effects are related to the presence of phospholipase A_2 enzymes, serino- and metalloproteases, L-amino acid oxidases, nucleotidases and others[11].

The *Micrurus* genus comprises 18 species, distributed throughout all the national territory and popularly known as "coral" and "coral-verdadeira". Elapidic accidents correspond to only 0.4% of accidents with venomous snakes registered in Brazil. The venom is constituted of presynaptic and postsynaptic neurotoxins, which respectively block the release of acetylcholine or compete with acetylcholine for cholinergic receptors on the neuromuscular junction, causing muscular weakness and paralysis. Due to the low molecular weight of the toxins, they are quickly absorbed to the systemic circulation and diffused to the tissues, and that explains why the symptoms of envenomation may appear fast, in less than an hour after the bite. The clinical progression to acute respiratory insufficiency is the cause of death in this type of envenomation[6].

The studies evaluating the effect of plants or plant derivates on snake envenomation are performed with different methodologies. Snakebite is often mimicked by injections of the snake venom in animals and the herbal preparation is administrated either before or after the administration of the venom, mostly orally or per injection. However, in some studies, the herbal compound is administered after *in vitro* preincubation. In this review, there were found 94 articles that tested determined antiophidic properties of one or more plant species (Table 1). A total of 104 plant species were reported, belonging to 51 different families. The most cited plant families in the reports were *Leguminosae* (20), *Compositae* (10), *Euphorbiaceae* (8), *Melastomataceae* (8), *Zingiberaceae* (8), *Salicaceae* (7), *Apocynaceae* (7), *Heliconiaceae* (5) and

Lamiaceae (5). The most cited plant species were *Casearia sylvestris* Sw. (6), *Eclipta prostrata* (L.) L. (5), *Mikania glomerata* Spreng. (4), *Schizolobium parahyba* (Vell.) S.F.Blake (4), *Curcuma longa* L. (4), *Tabernaemontana catharinensis* A.DC. (3), *Kalanchoe laciniata* (L.) DC. (3), *Jatropha gossypiifolia* L. (3), *Marsypianthes chamaedrys* (Vahl) Kuntze (3), *Bellucia dichotoma* Cogn. (3) and *Renealmia alpinia* (Rottb.) Maas (3).

Table 1. Plant species reported to treat snakebites in Brazil organized by family in alphabetical order. Each plant species is correlated with the species of the snake whose venom was used to test the antiophidic activity, as well as its mode of use, the plant part of choice, the number of articles reporting this use and the sources of the reports.

Plant species by family	Snake	Mode of use	Plant part	N° articles	References
Acanthaceae					
Justicia pectoralis Jacq.	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Amaranthaceae					
Alternanthera brasiliana (L.) Kuntze	*Bothrops jararaca*	Aqueous extract	Flowers	1	(Moura et al., 2015)[12]
Blutaparon portulacoides (A.St.-Hil.) Mears	*Bothrops jararacussu*	Ethanolic extract	Aerial parts	1	(Pereira et al., 2009)[13]
Annonaceae					
Annona montana Macfad.	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Annona muricata L.	*Lachesis muta rhombeata*	Aqueous extract	Leaves	1	(Cremonez et al., 2016)[14]
Apocynaceae					
Tabernaemontana catharinensis A.DC.	*Crotalus durissus terrificus*[15,17] *Bothrops jararacussu*[16]	Aqueous extract[15,16,17] Crude ethanolic extract[15]	Root bark	3	(Batina et al., 2000)[15] (Veronese et al., 2005)[16] (Almeida et al., 2004)[17]
Mandevilla illustris (Vell.) Woodson	*Crotalus durissus terrificus*	Aqueous extract	Subterranean system	1	(Biondo et al., 2004)[18]
Mandevilla pohliana (Stadelm.) A.H.Gentry	*Bothrops jararacussu, Bothrops moojeni, Bothrops alternatus, Bothrops pirajai, C. d. terrificus*	Aqueous extract	Leaves and stems, subterranean system	1	(Biondo et al., 2003)[19]

Fernaldia pandurata (A.DC.) Woodson	*Lachesis muta*	Aqueous extract	Roots	1	(De Paula et al., 2010)[11]
Tabernaemontana hystrix Steud.	*Crotalus durissus terrificus*	Aqueous extract	Root bark	1	(Batina; Giglio; Sampaio, 1997)[20]
Araceae					
Dracontium dubium Kunth	*Bothrops asper*	Ethanolic extract	Tubers	1	(Caro et al., 2017)[21]
Dracontium spruceanum (Schott) G.H.Zhu	*Bothrops atrox*	Aqueous extract	Bulbs	1	(Lovera et al., 2006)[22]
Philodendron megalophyllum Schott	*Bothrops jararaca*	Aqueous extract	Vine	1	(Moura et al., 2015)[12]
Arecaceae					
Euterpe oleracea Mart.	*Bothrops jararaca*	Aqueous extract	Unripe fruit	1	(Moura et al., 2015)[12]
Aristolochiaceae					
Aristolochia cymbifera Mart.	*Bothrops alternatus*	Aqueous-isopropanol extracts	Leaves	1	(Melo; Lúcia; Habermehl, 2007)[23]
Asteraceae					
Mikania glomerata Spreng.	*Crotalus durissus terrificus*[24,26] *Bothrops jararaca*[25] *Bothrops jararacussu, Bothrops moojeni, Bothrops alternatus, Bothrops neuwiedi*[26] *Lachesis muta*[11]	Aqueous extract[11,24,26] Hydroalcoholic extract[25]	Leaves[24,25,26] Roots[11,26] Stems[26]	4	(Floriano et al., 2009)[24] (Mourao et al., 2014)[25] (Maiorano et al., 2005)[26] (De Paula et al., 2010)[11]
Bignoniaceae					
Tabebuia aurea (Silva Manso) Benth. & Hook.f. ex S.Moore	*Bothrops mattogrossensis*[27] *Bothrops neuwiedi*[28]	Hydroalcoholic extract	Stem barks	2	(Malange et al., 2019)[27] (Reis et al., 2014)[28]
Fridericia chica (Bonpl.) L.G.Lohmann	*Crotalus durissus ruruima, Bothrops* atrox	Aqueous extract	Leaves	1	(Oliveira et al., 2009)[29]
Handroanthus barbatus (E.Mey.) Mattos	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Boraginaceae					
Cordia curassavica (Jacq.) Roem. & Schult.	*B. jararacussu*	Methanolic extract	Leaves	1	(Ticli et al., 2005)[30]
Capparaceae					
Crateva tapia L.	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Clusiaceae					

Clusia fluminensis Planch. & Triana	*Bothrops jararaca*	Different organic extracts	Leaves, stem, flowers, fruit (green and mature)	1	(Oliveira et al., 2014)[31]
Combretaceae					
Combretum leprosum Mart.	*Bothrops jararaca*, *Bothrops jararacussu*	Ethanolic extract	Roots	1	(Fernandes et al., 2014)[32]
Terminalia fagifolia Mart.	*Bothrops jararacussu*	Hydroalcoholic extract	Stem barks	1	(Tribuiani et al., 2017)[33]
Compositae					
Eclipta prostrata (L.) L.	*Bothrops jararaca*[34,35] *Bothrops jararacussu*[34,35,36] *Lachesis muta*[11,34] *Crotalus durissus terrificus*[36,37]	Aqueous extract[11,34,36] Ethanolic extract[35,37]	Aerial parts[32,36,37] NI[35] Roots[11,36]	5	(Melo et al., 1994)[34] (Patrão-neto et al., 2013)[35] (Diogo et al., 2009)[36] (Mors et al., 1989)[37] (De Paula et al., 2010)[11]
Baccharis oxyodonta DC.	*Crotalus durissus terrificus*	Methanolic extract	Aerial parts (twigs and leaves)	1	(Toyama et al., 2014)[38]
Baccharis trimera (Less.) DC.	*Bothrops* sp	Chloroform/methanol (2:1, v/v) extract	Aerial parts	1	(Januário et al., 2004)[39]
Chaptalia nutans (L.) Polák	*Bothrops asper*	Aqueous extract	Leaves	1	(Badilla et al., 2006)[40]
Calendula officinalis L.	*Bothrops alternatus*	Ointment 10% and ar-turmerone 10%	-	1	(Melo et al., 2005)[41]
Ayapana triplinervis (Vahl) R.M.King & H.Rob.	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Connaraceae					
Connarus favosus Planch.	*Bothrops atrox*[42] *Bothrops jararaca*[12]	Aqueous extract	Inner bark	2	(Silva et al., 2016)[42] (Moura et al., 2015)[12]
Costaceae					
Costus spicatus (Jacq.) Sw.	*Bothrops atrox*	Aqueous extract	Leaves	1	(Picanço et al., 2016)[43]
Crassulaceae					
Kalanchoe laciniata (L.) DC.	*Bothrops jararaca*[12,44] *Bothrops alternatus*[45]	Hydroethanolic extract[44] Aqueous extract[12,45]	Leaves[12,44] Aerial parts[45]	3	(Fernandes et al., 2017)[44] (Fonseca et al., 2004)[45] (Moura et al., 2015)[12]
Bryophyllum pinnatum (Lam.) Oken	*Bothrops jararaca*	Hydroethanolic extract	Leaves	1	(Fernandes et al., 2017)[44]
Dilleniaceae					

Davilla elliptica A.St.-Hil.	*Bothrops jararaca*	Chloroform[46] Methanol extracts[46,47]	Leaves	2	(Nishijima et al., 2009)[46] (Nishijima et al., 2015)[47]
Erythroxylaceae					
Erythroxylum ovalifolium Peyr.	*Lachesis muta*	Ethanolic extract	Stems	1	(Oliveira et al., 2016)[48]
Erythroxylum subsessile (Mart.) O.E.Schulz	*Lachesis muta*	Ethanolic extract	Stems	1	(Oliveira et al., 2016)[48]
Euphorbiaceae					
Jatropha gossypiifolia L.	*Bothrops erythromelas*[49,50] *Bothrops jararaca*[51]	Aqueous extract	Leaves	3	(Félix-Silva et al,. 2018)[49] (Félix-Silva et al., 2017)[50] (Félix-Silva et al., 2014)[51]
Jatropha mollissima (Pohl) Baill.	*Bothrops erythromelas*[49,52] *Bothrops jararaca*[52]	Aqueous extract	Leaves	2	(Félix-Silva et al,. 2018)[49] (Gomes et al., 2016)[52]
Croton urucurana Baill.	*Bothrops jararaca*	Aqueous extract	Stem barks	1	(Esmeraldino; Souza; Sampaio, 2005)[53]
Jatropha elliptica (Pohl) Oken	*Lachesis muta*	Aqueous extract	Leaves, stems	1	(De Paula et al., 2010)[11]
Manihot esculenta Crantz	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Fabaceae					
Libidibia ferrea (Mart. ex Tul.) L.P.Queiroz var. *ferrea*	*Bothrops jararaca*	Aqueous extract	Seeds	1	(Moura et al., 2015)[12]
Heliconiaceae					
Heliconia rostrata Ruiz & Pav.	*Bothrops asper*	Ethanolic extract	Rhizomes	1	(Estrada et al., 2010)[54]
Heliconia psittacorum L.f.	*Bothrops asper*	Ethanolic extract	Rhizomes	1	(Estrada et al., 2010)[54]
Heliconia curtispatha Petersen	*Bothrops asper*	Ethanolic extract	Rhizomes	1	(Pereañez et al., 2008)[55]
Heliconia wagneriana Petersen	*Bothrops asper*	Ethanolic extract	Rhizomes	1	(Pereañez et al., 2008)[55]
Heliconia latispatha Benth.	*Bothrops asper*	Ethanolic extract	Rhizomes	1	(Pereañez et al., 2008)[55]
Hypericaceae					
Hypericum brasiliense Choisy	*Crotalus durissus terrificus*[56] *Bothrops jararaca*[57]	Ethanolic extract	Leaves[56] Whole plant[57]	2	(Belo et al., 2013)[56] (Assafim et al., 2011)[57]
Icacinaceae					

Casimirella ampla (Miers) R.A.Howard	*Bothrops jararaca*, *Bothrops jararacussu*, *Bothrops atrox*	Ethanolic extract	Roots	1	(Strauch et al., 2013)[58]
Lamiaceae					
Marsypianthes chamaedrys (Vahl) Kuntze	*Bothrops atrox*[59] *Bothrops jararaca*[12,60]	Crushed leaves and crushed inflorescence without solvents[59] Aqueous extract[12,60]	Aerial parts (leaves and inflorescence)[59,60] Leaves[12]	3	(Magalhães et al., 2011)[59] (Castro et al., 2003)[60] (Moura et al., 2015)[12]
Clinopodium vimineum (L.) Kuntze	*Bothrops asper*	Aqueous extract	Leaves	1	(Badilla et al., 2006)[40]
Plectranthus monostachyus (P.Beauv.) B.J.Pollard	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Lauraceae					
Aniba parviflora (Meisn.) Mez	*Bothrops atrox*[61] *Bothrops jararaca*[12]	Aqueous and hydroalcoholic extract and extract of the residue from hydrodistillation of the leaf[61] Aqueous extract[12]	Leaves and bark[61] Bark[12]	2	(Moura et al., 2018)[61] (Moura et al., 2015)[12]
Leguminosae					
Plathymenia reticulata Benth.	*Bothrops atrox*[62] *Bothrops jararaca*[12]	Aqueous extract	Bark	2	(Moura et al., 2016)[62] (Moura et al., 2015)[12]
Abarema cochliocarpos (Gomes) Barneby & J.W.Grimes	*Bothrops leucurus*	Hydroethanolic extract	Stem barks	1	(Saturnino-Oliveira et al., 2014)[63]
Dipteryx alata Vogel	*Bothrops jararacussu*[64,65] *Crotalus durissus terrificus*	Hydroalcoholic extract	Bark	2	(Ferraz et al., 2014)[64] (Nazato et al., 2010)[65]
Harpalyce brasiliana Benth.	*Bothrops pirajai*[65]	Ethanolic extract	Leaves	1	(Ximenes et al., 2012)[66]
Schizolobium parahyba (Vell.) S.F.Blake	*Bothrops*[67] *Bothrops pauloensis* e *Crotalus durissus terrificus*[68] *Bothrops jararaca*[69] *Bothrops alternatus*, *Bothrops moojeni*[70]	Aqueous extract	Leaves	4	(Vale et al., 2011)[67] (Mendes et al., 2008)[68] (Martines et al., 2014)[69] (Vale et al., 2008)[70]
Pentaclethra macroloba (Willd.) Kuntze	*Bothrops* spp.[71,72] *Crotalus durissus terrificus*, *Crotalus atrox*, *Calloselasma rhodostoma*[72]	Aqueous extract	Barks	2	(Silva et al., 2007)[71] (Silva et al., 2005)[72]
Glycyrrhiza glabra L.	*Bothrops jararaca*	-	Roots	1	(Assafim et al., 2009)[73]

Bauhinia forficata Link	*Bothrops jararacussu, Crotalus durissus terrificus*	Aqueous extract	Aerial parts	1	(Oliveira et al., 2005)[74]
Brownea rosa-de-monte Bergius	*Bothrops asper*	Ethanolic extract	Leaves	1	(Salazar et al., 2014)[75]
Brongniartia podalyrioides Kunth	*Bothrops atrox*	Edunol in 0.9% saline containing Tween 20	Roots	1	(Reyes-Chilpa et al., 1994)[76]
Stryphnodendron adstringens (Mart.) Coville	*Lachesis muta*	Aqueous extract	Roots	1	(De Paula et al., 2010)[11]
Cassia fistula L.	*Bothrops jararaca*	Aqueous extract	Seeds	1	(Moura et al., 2015)[12]
Dipteryx odorata (Aubl.) Willd.	*Bothrops jararaca*	Aqueous extract	Seeds	1	(Moura et al., 2015)[12]
Machaerium ferox (Benth.) Ducke	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Loasaceae					
Nasa speciosa (Donn.Sm.) Weigend	*Bothrops asper*	Aqueous extract	Leaves	1	(Badilla et al., 2006)[40]
Loganiaceae					
Strychnos pseudoquina A. St.-Hil.	*Bothrops jararaca*	Dichloromethane and metanol extracts	Leaves	1	(Nishijima et al., 2009)[46]
Malpighiaceae					
Byrsonima crassa Nied.	*Bothrops jararaca*	Chloroform and metanol extracts	Leaves	1	(Nishijima et al., 2009)[46]
Malvaceae					
Pachira glabra Pasq.	*Bothropoides pauloensis*	Hexanoic extract	Stem bark and root bark	1	(Mendes et al., 2013)[77]
Gossypium hirsutum L.	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Melastomataceae					
Bellucia dichotoma Cogn.	*Bothrops atrox*[78,79] *Bothrops jararaca*[12]	Aqueous extract	Bark	3	(Moura et al., 2017)[78] (Moura et al., 2014)[79] (Moura et al., 2015)[12]
Mouriri pusa Gardner ex Gardner	*Bothrops jararaca*	Dichloromethane and metanol extracts	Leaves	1	(Nishijima et al., 2009)[46]
Miconia fallax DC.	*Lachesis muta*	Aqueous extract	Stems	1	(De Paula et al., 2010)[11]
Miconia albicans (Sw.) Steud.	*Lachesis muta*	Aqueous extract	Stems	1	(De Paula et al., 2010)[11]
Miconia sellowiana Naudin	*Lachesis muta*	Aqueous extract	Not determined	1	(De Paula et al., 2010)[11]
Tibouchina stenocarpa (DC.) Cogn.	*Lachesis muta*	Aqueous extract	Roots	1	(De Paula et al., 2010)[11]

Meliaceae					
Swietenia macrophylla King	*Bothrops asper*, *Bothrops marmoratus*	-	-	1	(Arias et al., 2019)[80]
Menispermaceae					
Cissampelos pareira L.	*Bothrops diporus*	Aqueous, ethanolic and hexanoic extracts	Leaves, flowers, tender stems, and roots	1	(Verrastro et al., 2018)[81]
Moraceae					
Morus nigra L.	*Bothrops jararacussu*	Ethanolic extract	Leaves	1	(Ribeiro et al., 2019)[82]
Musaceae					
Musa × *paradisiaca* L.	*Bothrops jararacussu*, *Bothrops neuwiedi*, *Crotalus durissus terrificus*	Plant exudates	Pseudo stems	1	(Borges et al., 2005)[83]
Piperaceae					
Peperomia obtusifolia (L.) A.Dietr.	*Crotalus durissus terrificus*	Methanolic extract	Aerial parts	1	(Tamayose et al., 2017)[84]
Piper umbellatum L.	*Bothrops asper*, *Bothrops atrox*	Organic extract	Branches	1	(Núñez et al., 2005)[85]
Piper peltatum L.	*Bothrops asper*, *Bothrops atrox*	Organic extract	Branches	1	(Núñez et al., 2005)[85]
Polygalaceae					
Bredemeyera floribunda Willd.	*Bothrops jararacussu*	Ethanolic extract	Roots	1	(Alves et al., 2019)[86]
Portulacaceae					
Portulaca pilosa L.	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Primulaceae					
Myrsine parvifolia A. DC.	*Bothrops jararaca*	Hydroethanolic extract, hexane extract, dichloromethane extract, ethyl acetate extract, n-butanol extract, aqueous crude extract	Leaves	1	(Corrêa et al., 2018)[87]
Rubiaceae					
Uncaria tomentosa (Willd. ex Schult.) DC.	*Bothrops asper*	Aqueous extract	Roots	1	(Badilla et al., 2006)[40]
Salicaceae					
Casearia sylvestris Sw.	*Bothrops jararacussu*[88,89,90,91,92] *C. durissus terrificus*[89,91] *B. pirajai*, [89,90]	Aqueous extract Aqueous and hydroalcoholic (70%) extracts[92]	Leaves Roots[11]	6	(Silva et al., 2008)[88] (Cavalcante et al., 2007)[89] (Borges et al., 2001)[90] (Borges et al., 2000)[91]

	B. moojeni[89,90,91] *Bothrops neuwiedi* and *Bothrops asper*[90,91] *Micrurus frontalis*[91] *Lachesis muta*[11]				(De Paula et al., 2010)[11] (Oshima-franco et al., 2005)[92]
Casearia mariquitensis Kunth	*Bothrops neuwiedi pauloensis*	Aqueous extract	Leaves	1	(Izidoro et al., 2003)[93]
Salviniaceae					
Salvinia sp.	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Sapindaceae					
Sapindus saponaria L.	*Bothrops jararacussu*, *Bothrops moojeni*, *Bothrops alternates* e *Crotalus durissus terrificus*[94] *Lachesis muta*[11]	Several extracts with different solvents[94] Aqueous extract[11]	*In vitro* cultivated callus[94] Roots[11]	2	(Silva et al., 2011)[94] (De Paula et al., 2010)[11]
Sapotaceae					
Manilkara subsericea (Mart.) Dubard	*Lachesis muta*	Ethanol, hexane, ethyl acetate, or dichloromethane	Leaves and stems	1	(Oliveira et al., 2014)[95]
Solanaceae					
Solanum campaniforme Roem. & Schult.	*Bothrops pauloensis*	Ethanolic extract	Leaves	2	(Torres et al., 2013)[96] (Torres et al., 2011)[97]
Urticaceae					
Urera baccifera (L.) Gaudich. ex Wedd.	*Bothrops asper*	Aqueous extract	Leaves	1	(Badilla et al., 2006)[40]
Urtica leptophylla Kunth	*Bothrops asper*	Aqueous extract	Leaves	1	(Badilla et al., 2006)[40]
Velloziaceae					
Vellozia squamata Pohl	*Bothrops jararacussu*	Hydroalcoholic extract	Leaves	1	(Tribuiani et al., 2014)[98]
Verbenaceae					
Lippia gracilis Schauer	*Bothrops jararaca*	Aqueous extract	Leaves	1	(Moura et al., 2015)[12]
Vochysiaceae					
Vochysia haenkeana Mart.	*Bothrops jararacussu*	Hydroalcoholic extract	Stem barks	1	(Harder et al., 2017)[99]
Zingiberaceae					

Hedychium coronarium J.Koenig	*Lachesis muta, Bothrops atrox, Bothrops moojeni*	Essential oils	Leaves and rhizomes	1	(Miranda et al., 2014)[100]
Curcuma longa L.	*Bothrops jararaca, Crotalus durissus terrificus*[101] *Bothrops alternatus*[23,41,45]	Hexane extract[101] Aqueous-isopropanol extracts[23,41] Methanolic extract[41] Aqueous extract[45]	Rhizomes	4	(Ferreira et al., 1992)[101] (Melo; Lúcia; Habermehl, 2007)[23] (Melo et al., 2005)[41] (Fonseca et al., 2004)[45]
Renealmia alpinia (Rottb.) Maas	*Bothrops asper*	Ethanolic extract[102,103] Dichloromethane extract[104]	Leaves[102,104] Leaves (wild) and whole plant (*in vitro*)[103]	3	(Patiño et al., 2012)[102] (Patiño et al., 2015)[103] (Gómez-Betancur et al., 2014)[104]

Casearia sylvestris Sw. (*Salicaceae*), popularly known in Brazil as "guaçatonga", is widely used in folk medicine as an antiseptic, wound healer, topical anesthetic, and antitumor, antiulcer and antiophidic[105,106]. Borges et al. (2000) concluded that the aqueous extract of *C. sylvestris* inhibits the enzymatic and toxic activities of various snake venoms and the toxic phospholipases A2 isolated from these venoms after preincubation of the extract with the venom or isolated toxins in the ratios (w:w): 1:1, 1:5, 1:10, 1:20 and 1:25 (venom/toxin to plant extract)[91]. In another study, Borges et al. (2001) discovered that the aqueous extract of this plant contains compounds that neutralize proteases present in snake venoms[90]. After preincubation of a myotoxin from *B. jararacussu* venom with the hydroalcoholic extract from *C. sylvestris* (4 mg/ml), a prevention of the neuromuscular blockade caused by the toxin was achieved (Oshima-Franco et al., 2005). This protection may be mediated by compounds such as flavonoids and phenols identified by thin-layer chromatography and colorimetric assays[92]. Other studies expanded the spectrum of C. *sylvestris* antivenom activities[88,89]. Silva et al. (2008) isolated a few compounds from the plant that are responsible for the inhibition of B. *jararacussu* venom toxic effects characterized them as four ellagic acid derivatives[88].

Eclipta prostrata (L.) L. (Compositae), popularly known in Brazil as "erva-botão" is a source of several secondary metabolites, such as polypeptides, polyacethylenes and triterpenes[107] flavonoids, phytosterols and coumestans[108]. Coumestans are an important class of natural oxygenated aromatic products, including wedelolactone and its

demethylated form, demethylwedelolactone, both responsible for the main medicinal effects of *E. prostrata*, such as its antihepatotoxic, antihypertensive, antitumor, antiphospholipase A2 and antidote activities against snake venoms.[107,109,110]. Neutralization of the lethal activity of the venom of *C. durissus terrificus* and protection against its myotoxic effects was observed with ethanolic extracts of *E. prostrata* when mixed with the venom prior to injection into adult mice (Mors et al., 1989). This neutralization was attributed to three compounds: wedelolactone, sitosterol and stigmasterol[37]. These findings were afterwards also observed in another study (Melo et al., 1994). The *in vitro* myotoxicity was neutralized by simultaneous exposure of the muscles to an aqueous extract of *E. prostrata* or to wedelolactone. Sitosterol and stigmasterol were less effective than wedelolactone, but interacted synergistically with it. The *in vivo* myotoxicity was neutralized by preincubation of the venom with the E. *prostrata* extract or wedelolactone prior to injection into mice. These effects were interpreted as consequences of antiproteolytic and antiphospholipase A2 activities of *E. prostrata* and its constituents[34]. Diogo et al. (2009) genetically modified *E. prostrata* aiming to produce secondary metabolites with pharmacological properties against phospholipase A2 and the myotoxic activities of snake venom. The best effect was that of the clone and isolated coumestans (wedelolactone and demethylwedelolactone) which inhibited the myotoxic activity induced by basic phospholipases A2[36]. The antiophidic effect of the *E. prostrata* was lastly also investigated by Patrão-Neto et al. (2013) using *in vitro* and *in vivo* experimental protocols that showed the ability of the plant extract in preventing the induction of edema and muscle damage. Besides, its association with the steroidal anti-inflammatory drug dexamethasone showed additive effect[35].

Mikania glomerata Spreng. (Asteraceae) popularly known as "guaco", shows many pharmacological activities, among them antifungal, antimicrobian, bronchodilator, antiallergic, anti-inflammatory and antiophidic[111,112,113]. When preincubated with the venoms at various ratios (w/w), aqueous extracts of *M. glomerata* were able to efficiently neutralize different toxic, pharmacological, and enzymatic effects induced by venoms from *Bothrops* and *Crotalus* (Maiorano et al., 2005). Phospholipase A2 activity and the edema induced by *C. durissus terrificus* venom were inhibited around 100 and ∼40%, respectively, although this inhibition was only partial for *Bothrops* venoms. The haemorrhagic activity of *Bothrops* venoms was significantly inhibited by this vegetal species, while the clotting activity of *C. durissus terrificus*, *B. jararacussu*, and *B.*

neuwiedi venoms was totally inhibited[26]. Floriano et al. (2009) evaluated the clinical and laboratory aspects of *C. durissus terrificus* experimental envenomation in Wistar rats treated with antivenom and the aqueous extract of *M. glomerata*. A faster recovery from sedation was observed only for animals of the group receiving venom+antivenom+*M. glomerata* 10% orally when compared to the group receiving venom+antivenom[24]. Mourao et al. (2014) investigated the effects of hydroalcoholic extract of *M. glomerata* on the activity of *B. jararaca* snake venom in Wistar rats and found out that the administration of the venom incubated with the extract at proportions of 1:1, 1:2 and 1:4 promoted a significant reduction in the number of inflammatory cells and a marked decrease in edema. There was also a significant reduction in the intensity of haemorrhagy in animals receiving the snake venom incubated with the extract, with the observation of a progressive and parallel inhibition with increasing proportion of *M. glomerata*[25].

De Paula et al. (2010) demonstrated the ability of different aqueous plant extracts, including *C. sylvestris*, *E. prostrata* and *M. glomerata* to neutralize the following biological effects of *Lachesis muta* snake venom: hemolysis, haemorrhagic, clotting and proteolytic. Plant extracts were preincubated for 30 minutes with *L. muta* venom at 1:10 ratio (venom:plant, w/w) and then tested these activities by *in vitro* and *in vivo* assays. They concluded that vegetal extracts appear to be an alternative treatment against local damage to complement the serum therapy or may be useful as prototypes for designing new antiophidian molecules to improve the current treatment used for *L. muta* bites[11].

Schizolobium parahyba (Vell.) S.F.Blake (Leguminosae), a plant found in Atlantic Forest in southestern Brazil, and popularly called “guapuruvú”, is used in form of teas and infusions against ophidian envenomation by people of the Triângulo Mineiro region (Minas Gerais, Brazil)[70]. The aqueous extract prepared from *S. parahyba* was tested *in vitro* and *in vivo* to analyse its ability to inhibit some biological and enzymatic activities induced by *B. alternatus* and *B. moojeni* snake venoms (Vale et al., 2008). *S. parahyba* inhibited 100% of lethality, blood incoagulability, haemorrhagic and indirect haemolytic activities at a 1:10 ratio (venom/extract, w/w), as well as coagulant activity at a 1:5 ratio (venom/ extract, w/w) induced by both venoms[70]. Mendes et al. (2008) found out that *S. parahyba* aqueous extract was very effective in inhibiting phospholipase A2, coagulant, fibrinogenolytic, haemorrhagic and myotoxic activities induced by *B. pauloensis* and *C. durissus terrificus* venoms, as well as the effects of some isolated toxins when previously incubated with these venoms and toxins at different ratios before *in vitro*

and *in vivo* assays. They obtained also a reduction in the decrease of platelet number and plasma fibrinogen concentration during *in vivo* assays and concluded that their observations confirmed the potent snake venom neutralizing properties of this plant and that it might be used as an alternative treatment to serum therapy and as a rich source of potential toxin inhibitors[68]. Vale et al. (2011) isolated and identified four flavonoids (isoquercitrin, myricetin-3-O-glucoside, catechin and gallocatechin) from *S. parahyba* and tested them against hemorrhagic, myotoxic and fibrinogenolytic activities of *Bothrops* venoms and isolated metalloproteinases. The results showed that gallocatechin and myricetin-3-O-glucoside are good inhibitors of haemorrhagic and fibrinogenolytic activities of metalloproteinases, respectively. Gallocatechin also inhibited the myotoxic activity of both *B. alternatus* venom and phospholipase A2 from *B. neuwiedi*[67].However, another study (Martines et al., 2014) tested the immediate intravenous infusion of 2.0 mg/kg of *S. parahyba* aqueous extract after intravenous *Bothrops* venom administration in rats and obtained no protection against the systemic and renal actions of the venom in the animals, indicating that the plant extract is likely ineffective against Bothropic venom when it reaches the blood stream. These results raise concerns on the clinical utility of *S. parahyba* as a therapy against venom systemic effects. The local use of the extract on a bite site might be useful as an adjuvant therapy against local inflammatory and necrotic injury[69].

Curcuma longa L. (Zingiberaceae), popularly known as "açafrão", is known to contain components able to inhibit platelet aggregation both *in vitro* and *in vivo*, and decrease hyperlipidemia in mice[114]. Its roots are used in Brazil against insect bites and allergic reactions observed after skin contact with caterpillars[101]. A potent antivenom against snakebite was isolated from *C. longa* (Ferreira et al., 1992). The fraction consisting of ar-turmerone neutralized both the haemorrhagic activity present in *B. jararaca* venom, and the lethal effect of *C. durissus terrificus* venom when mixed with the venom in multiple concentrations prior to injection in mice[101]. Fonseca et al. (2004) tested topical application of a concentrated aqueous extract from *C. longa* after inoculation of *B. alternatus* venom in mice and obtained satisfactory results in the local effects of the toxins, such as edema reduction, haemorrhagic halo and necrosis prevention[45]. The efficiency of *C. longa* extracts and ar-turmerone against the local effects of bothropic envenomation was also furthermore investigated in another study (Melo et al., 2005). *B.s alternatus* venom was inoculated into rabbits. The animals were

divided in groups receiving: subcutaneous application of *C. longa* extract (1.0 ml); topic treatment of *C. longa* hydroalcoholic extract (1.0 ml); topic application of ar-turmerone in vaseline (1.0 g); or topic application of *C. longa* methanolic extract (1.0 ml). The most efficient treatment was the topic application of ar-turmerone, which showed evident decrease of haemorrhagic halo in skin, smaller edema degree and completely recover (necrosis absence)[41]. Melo and Habermehl, (2007) also evaluated the therapeutic efficacy of extracts from *C. longa* using bothropic envenomation as experimental model in rabbits and concluded that topic application of the extract was the most effective treatment against local symptoms (edema, haemorrhages and necrosis) caused by *B. alternatus* snake envenomation[23].

Tabernaemontana catharinensis A.DC. (Apocynaceae), popularly known as 'leiteiro de vaca', is a small tree occurring in Argentina, Paraguay, Bolivia and southern Brazil. It is used as antidote in folk medicine by being applied to the site of the snake bite and believed to neutralize the effect of the venom[15]. Batina et al. (2000) reported the ability of the aqueous extract *T. catharinensis* to inhibit the lethal and myotoxic activities of *C. durissus terrificus* venom when injected in rats (10 mg/100 g) immediately after the injection of the venom and when incubated with the venom before injection in the animals. A pure compound (quaternary alkaloid 12-methoxy-4-methylvoachalotine), obtained from the fractioning of the ethanolic extract of the plant, showed a pronounced antiophidian activity, inhibiting 100% the lethality when injected 20 s after the venom[15]. Almeida et al. (2004) fractionated the aqueous extract of *T. catharinensis* and discovered that its antivenom activities are exerted by distinct substances present in fraction PVII, which contains 12-methoxy-4-methylvoachalotine as its major component[17]. Veronese et al. (2005) obtained partial neutralization of the myotoxic effect of *B. jararacussu* venom and two of its myotoxins by the aqueous extract of *T. catharinensis in vitro* and *in vivo* when the extract (2 mg) was pre-incubated with the venom or toxins before injection in rats[16].

Kalanchoe laciniata (L.) DC. (Crassulaceae) is indistinctively known in Brazil as "saião" and is widely used in traditional medicine for its antiinflammatory properties[115]. Several popular reports have indicated that this species could be useful for treating snakebites[44,12]. Fonseca et al. (2004) tested topical application of a concentrated aqueous extract from *K. laciniata* after inoculation of *B. alternatus* venom in mice and obtained satisfactory results in the local effects of the toxins, such as edema reduction, hemorrhagic

halo and necrosis prevention[45]. Extracts of *K. laciniata* preincubated with *B. jararaca* venom at a ratio of 1:48 (venom: plant, w/w) produced a significant reduction in haemorrhage when injected in mice (Moura et al., 2015)[12]. Fernandes et al. (2017) evaluated the antiophidic activity of *K. laciniata* against local effects induced by *B. jararaca* snake venom by intraperitoneal administration of (125, 250 and 500 mg/kg) hydroethanolic extract in mice in a pre-treatment protocol and obtained significant reduction of haemorrhagic activity and inhibition of phospholipase activity[44].

Jatropha gossypiifolia L. (Euphorbiaceae) is a medicinal plant popularly known in Brazil as "pinhão-roxo". It is largely used in folk medicine as antiophidic, antiinflammatory, antihemorrhagic, hemostatic and healing[51,116]. Félix-Silva et al. (2014) demonstrated that the aqueous extract of the plant, prepared by decoction, was able to inhibit enzymatic and biologic activities induced by *B. jararaca* snake venom *in vitro* and *in vivo*. The blood incoagulability was efficiently inhibited by oral administration of the extract. The hemorrhagic and edematogenic local effects were also inhibited in animals treated with extract by oral and intraperitoneal routes. The inhibition of myotoxic action reached almost 100%[51]. Another study (Félix-Silva et al., 2017) assessed the effectiveness of the aqueous extract of this plant and of the bothropic antivenom against local effects induced by *B. erythromelas* venom. Inhibition of edematogenic and hemorrhagic local effects were assayed in mice in pre- and pos-treatment protocols. Inhibition of proteolytic, phospholipase A2 and hyaluronidase enzymatic activities were evaluated *in vitro*. The results showed that in pre-treatment protocol the plant extract and bothropic antivenom presented very similar effects. However, bothropic antivenom poorly inhibited edema and hemorrhage in post-envenomation protocol, whilst, in contrast, the herbal extract was significantly active even when used after *B. erythromelas* venom injection, being able to inhibit all the tested enzymatic activities of the venom, while bothropic antivenom was active only against hyaluronidase activity, which could justify the low effectiveness of the antivenom against local effects *in vivo*. Together, these data indicate that, despite the presence of immunological cross-reactivity, brazilian polyvalent bothropic antivenom presented low inhibitory potential against biological and enzymatic effects of *B. erythromelas* venom, illustrating the need for new strategies in the production of antivenom with broad neutralizing potential in the treatment of *Bothrops* spp. envenomation throughout the country and highlight the antiophidic potential of *J. gossypiifolia*[50].

Marsypianthes chamaedrys (Vahl) Kuntze (Lamiaceae), popularly known as "boia-caá" ('snake herb' in Tupi), is used in the state of Amazonas both orally and as a poultice at the site of the snakebite to alleviate the secondary effects of the venom[116]. Castro et al. (2003) showed that the aqueous extract of *M. chamaedrys* inhibited fibrino clotting induced by several snake venoms in an *in vitro* preliminary study. These data indicate that this extract affected thrombin-like enzymes[60]. *M.s chamaedrys* was also tested *in vitro* to determine its ability to block indirect phospholipase A2 and direct coagulant activities and *in vivo* to determine its ability to inhibit leukocyte migration and cytokine release (Magalhães et al., 2011). *In vitro*, it showed antiphospholipase A2 and anticoagulant activities. *In vivo*, *M. chamaedrys* inhibited leukocyte migration and the release of the proinflammatory cytokines. Of the extracts used, those obtained from the crushed plant had the greater inhibitory activity in *in vitro* tests, showing that biological activity is affected by the way extracts are obtained[59].

Bellucia dichotoma Cogn. (Melastomataceae), which is popularly known as "muúba" or "goiaba-de-anta", is used in alternative medicine in the form of a tea to treat snake bites in communities in the west of the state of Pará[117]. One study compared inhibition of the local effects of *B. atrox* venom by aqueous extract of *B. dichotoma* administered according to traditional methods and pre-incubated with the venom (Moura et al., 2014). Haemorrhagic, phospholipase A2 activity and edema were completely inhibited using the pre-incubation protocol. In the tests simulating traditional use, i.e., oral administration of the extract as pre- or post-treatment or in combination with the antivenom, the extract was more effective in inhibiting edema induced by the venom than the standard treatment. The most effective dose was 283.3 mg/kg. These results provide scientific evidence to support the use of *B. dichotoma* orally either as prophylaxis or after envenomation[79]. Moura et al. (2017) showed that the aqueous extracts inhibited 100% of the phospholipase and coagulant activity of *B. atrox* venom when pre-incubated. Without pre-incubation, however, there was no reduction in phospholipase activity, although significant inhibition of coagulant activity was observed. In the doses used in folk medicine (48.3, 145 and 289.8 mg/kg), without pre-incubation, both extracts inhibited 100% of the coagulant activity. *In vivo*, the extracts were unable to inhibit the defibrinating activity of the venom but were effective in inhibiting its edema-inducing activity[78].

Renealmia alpinia (Rottb.) Maas (Zingiberaceae), known as "guaiporé", has been used in the traditional medicine to treat snakebites[103,118,119]. The acute toxicity tests and analgesic activity of *R. alpinia* were evaluated *in vivo* (Patiño et al., 2012). In addition, tests were undertaken *in vitro* to demonstrate inhibition of coagulant, haemolytic and proteolytic activity of the *B. asper* venom. *R. alpinia* was an effective therapeutic alternative in association with antivenom treatment in the event of a *B. asper* snakebite accident. It was demonstrated to protect against the lethal effects and provided analgesic properties as well[102]. *R. alpinia* extract significantly inhibited the proteolytic activity and indirect hemolytic activity of *B. asper* venom at a venom: extract ratio of 1:20 (Gómez-Betancur et al., 2014). Moreover, the present data demonstrate that pinostrobin may mitigate some venom-induced local tissue damage due to hemorrhagic effects, and the compound is also responsible for the analgesic and anti-inflammatory activity of the extract[104]. Patiño et al. (2015) shows that *R. alpinia* wild and *in vitro* extracts partially inhibited lethal and systemic hemorrhagic activities of *B. asper* venom, in a model with extract administration before venom injection[103].

5. Conclusions

In this review, out of 104 plant species used to treat snakebite in Brazil, only eleven species are reported at least three times, other eleven are reported twice and the other 82 species are each reported in just one study. The most cited plant species were *Casearia sylvestris* Sw., *Eclipta prostrata* (L.) L., *Mikania glomerata* Spreng., *Schizolobium parahyba* (Vell.) S.F.Blake, *Curcuma longa* L., *Tabernaemontana catharinensis* A.DC., *Kalanchoe laciniata* (L.) DC., *Jatropha gossypiifolia* L., *Marsypianthes chamaedrys* (Vahl) Kuntze, *Bellucia dichotoma* Cogn., and *Renealmia alpinia* (Rottb.) Maas.

In regions where no antiserum treatment is possible or it is difficult, preparations of plants could play an important role in the treatment of this neglected health issue. Further studies on the chemistry and pharmacology of traditionally used plant species will help understanding the role that snakebite herbal remedies can have within local medical health systems and may be useful in the development of alternative or complementary treatments to reduce the number of severe disabilities and deaths.

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TOXICON

An Interdisciplinary Journal on the Toxins Derived from Animals, Plants and Microorganisms

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Toxicon has an open access mirror *Toxicon: X*, sharing the same aims and scope, editorial team, submission system and rigorous peer review.

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