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Anti-venom Activity of Medicinal Plants from South America

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ABSTRACT

The use of plants to subdue or reverse the effects of snakebite has long been recognized. Plant extracts were widely used as therapy for snakebite by South American traditional healers, and especially in tropical regions where plant resources are diverse and plentiful. Several medicinal plants are also believed to have been used as a source of snakebite antidote. Reference to the use of plants as part of early indigenous ethnomedical practices appears in traditional drug recipes recovered from chronicles of Spanish explorers and includes evidence that methods were passed on orally through generations. The most frequently encountered poisonous snake genera found in regions of South America include: Bothrops (jarara/ lanceheads), Crotalus (casabel/rattlesnakes), Lachesis (surucucú/bushmasters) and Micrurus (coral). Coral snakes have very powerful venom but confrontation with these snakes is infrequent because of their quiet and secretive character. A bibliographic revision helped us identify more than one hundred seventy plants with anti-venom activity in South America. Most are identified using their common names, sometimes making it difficult to determine the formal taxonomic name. Furthermore, the absence of available references or other documentation to verify or even designate a proper scientific name continues to pose a problem. There have been

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numerous attempts to study and characterize the anti-venom activity in native plants. We show that modern methods that provide unequivocal identification of active compounds together with in vitro and in vivo assays have enabled both evaluation and validation of ancestral knowledge. Among the pharmacologically active secondary metabolites isolated from plants, flavonoids are most frequently cited inhibiting phospholipases, lipoxygenases and metalloproteases.

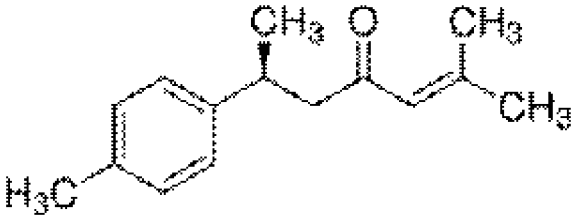
Keywords: **South American medicinal plants, *Bothrops*, Anti-venom activity.**

Introduction

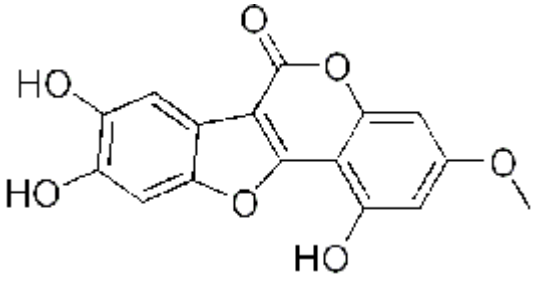
Effective treatment for bites and stings of venomous animals like snakes, spiders and scorpions has always been of great concern, and certainly remains so for persons in isolated rural areas where modern health care is not available. In the writings of colonial Spanish and even in modern texts, there are frequent references to the application of plant materials to treat bites and stings for a range of venomous animals. One may read that amazing and wonderful cures were possible using information gained, compiled, refined and enriched over the many years.

The oldest relevant South American record documenting the healing properties of plants was in 1711, "*Materia Médica Misionera por el hermano Pedro de Montenegro*". This manuscript describes and references the virtues and healing or curative properties of ca. 108 plants using their Spanish and vernacular names (Guarani or Tupi), the areas in which they are found and instructions for use. Specific instructions for 16 of these plants are provided for treatment of snakebites (Ricciardi *et al.*, 1996).

A number of other compounds with anti-venom activity were also reported. Among such compounds was the prenylated pterocarpan, (-)-edunol, isolated from the Fabaceae, *Brongniartia podalyrioides* Kunth. and *B. intermediate*: with structure and properties similar to the cabenegrines (Reyes-Chilpa *et al.*, 1994). Yet another was a compound whose activity was first recognized in studies with mice, *ar*-turmerone, a sesquiterpene from *Curcuma longa* (Zingiberaceae). This compound was shown to have anti-venom activity against venom of both *B. jararaca* and *Crotalus durissus terrificus* (Ferreira *et al.*, 1992). Wedelolactone is another compound isolated from *Eclipta prostrata* that antagonizes the poisonous effects of crotalid myotoxin, and in which an enzyme inhibitory mechaniam is likely (Melo, 1997; Melo *et al.*, 1993; Melo and Ownby, 1999).



ar-turmerone



wedelolactone

The increasing number of publications examining *in vitro* and *in vivo* interaction between extracts or isolated components of plants and snake venoms encourage review and discussion of the issue of inhibition or neutralization of the toxicity of these poisons by extracts, oils or various natural products.

Even today in regions where modern medical facilities are not available or easily accessible or affordable, traditional medicine remains as the primary form of health care. This type of health care also remains primarily based on ancestral knowledge. A clearer and deeper understanding of accumulated knowledge serving as a basis for these traditional methods should further validate potential usefulness. An understanding of mechanism of action for attenuation of venom toxicity will guide future research to further reduce ineffectiveness or danger (Farnsworth, 1988; Posey, 2002).

Snakebites

Risk of being bitten or stung by a snake constitutes a serious and frequent threat in South America. The incidence of snakebite for different regions of the world is summarized in Table 1.1. Both the incidence of poisonous bites and resulting number of deaths is high in Latin America (López Sáez and Perez Soto, 2009):

Table 1.1

Region	*Population*	*Nº Snakebites (x10⁸ inhabitants)*	*Nº Poisonings*	*N º Deads*
Europe	700	25,000	8,000	30
Near East	160	20,000	15,000	100
North America	270	45,000	6,500	15
Latin America	400	300,000	150,000	5,000
Africa	750	1,000,000	500,000	20,000
Asia	3,000	4,000,000	2,000,000	100,000
Oceania	20	10,000	3,000	200
Total	5,300	5,400,000	2,682,500	125,345

The poisonous action of venom is due to toxins and enzymes including: cardiotoxins (cytotoxins), disintegrins, hemotoxins, hemolysins, myotoxins, necrotoxins, nephrotoxins, neurotoxins, L-amino acid oxidase, phospholipases, adenesine triphosphatase, acetylcholinesterase, phosphodiesterases, proteases (hemorrhage-promoting) monoesterases (5'-nucleotidase), metalloproteinases, hyaluronidase, peptidase, deoxiribonucleasas, fibrin and fibrinogenolysinases, *L*-arginine ester hydrolase, coaglutinins, lectins.

The species of venomous snakes found in South America belong mainly to two families, Viperidae (solenoglyphous teeth, Figure 1.1A) and Elapidae (proteroglyphous teeth, Figure 1.1B). Genera frequently found within these two large families include *Bothrops*, *Crotalus*, *Lachesis* and *Micrurus*, and different species are found for each of these genera according to region.

Historical Background

Figure 1.1A: Dental structure of solenoglyphous teeth.

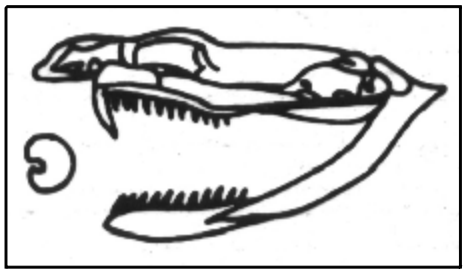


Figure 1.1B: Dental structure of proteroglyphous teeth.

As noted above, chronicles of colonial times describing aboriginal medicine or ethnomedicine in South America make numerous references to the use of plants for treatment of snakebites. The oldest such document in 1711 was that of Hermano Pedro de Montenegro of the Compañía de Jesús, and consisted of many handwritten sheets. The plant names and descriptions of that time are not always easy to equate with the most likely botanical species recognized today. Ricciardi *et al*. (1996) were able to identify some of the species referred to those having properties effective against snakebite in these documents: *Cyperus sesquiflorus*, *Cissampelos pareira* (*C. glaberrima*), *Sidastrum paniculatum*, *Asclepias mellodora* (*A. campestris*), *Euphorbia dichotoma*, *Dorstenia brasiliensis*, *Agrimonia eupatoria*, *Aristolochia rotunda*, *Gomphrena tuberous*, *Pilocarpus pennatifolius*.

Other medicinal plant historians include Antonio Ruiz de Montoya (1585-1652), Buenaventura Suárez (1679-1750) and Andreas Thevet who published his observations on medical practices of the Guarani in Brazil, *Les singularités de la France antarctique autrement nommée Amérique et des plusieurs terres et des decouvertes de notre temps*, reprinted in Paris in 1878. Jose Acosta (ca. 1539-1600) studied American flora and recorded his observations in *De natura novi orbis* which was later published in Salamanca in 1588. There were also numerous revisions of this work such as, *Historia Natural y Moral de las Indias* (Pedro Lozano, 1697-1752) a writer, historian and Spanish ecclesiastic who wrote on Chaco Valley. Like many American works of this period, the focus was mainly ethnographic detail. Noteworthy however, chapters on rivers and quality of land have extensive discussion of regional medicinal plants.

Plants Historically Considered Effective against Snakebite

This review aims to present and update information from current literature on traditional knowledge for snakebite treatment from plants. Different authors have given detailed accounts on various snakebite treatments found in plants (Reyes-Chilpa and Jiménez Estrada, 1995; Mors *et al.*, 2000; Ricciardi, 2005; López Sáez *et al.*, 2009; Makhija and Khamar, 2010; Abhijit and Jitendra, 2012). These reports provided a comprehensive view of the ability of a given snakebite treatment to relieve one or more complex symptoms such as pain, bleeding, swelling, infection, in some cases for more than one poison. Knowledge and use of plants for snakebite treatment is very old. Medical treatment by the Ayurvedic in India (centuries before the Christian era) includes 211 plants. The use of plants in Mexico preceded colonization by Spanish, and in the 16th century Francisco Hernandez was able to document 119 newly described plants in his *Historia de las plantas de la nueva España* (History of the New Spain plants). Also, in the 16th century Fray Bernardino de Sahagún cites the use of picietl or tobacco. Ethnic groups like the Colorados, Cayapa and Coaquier of

northern Ecuador used 40 species of Gesneriaceae, and the Colorados and Cayapa also used 11 species of Polypodial and 7 species of Piperaceae.

Reyes-Chilpa and Jiménez Estrada (1995), in writing about the Tepehuanos of Chihuahua noted that: "the indians rarely open wounds caused by snakebites. To cure the bite they depend on the application of specific mixtures prepared with differents plant materials."

Otero *et al*. (2000a, 2000b, 2000c), describe the use of more than 77 plants in Colombia in the form of beverages prepared by infusion, as alcohol extracts (30-38 per cent v/v) or by mixing various plant materials with rum. Other methods included decoction or maceration in water for topical or localized use. Esteso (1985) in his work *Ofidismo en la República Argentina* (Snakebite in Argentina) citing folklore, almost always referred to the statements of a respectable elderly such as a grandfather, whose knowledge passed from family to family.

López Sáez *et al*. (2009) cite use of the genus: *Aristolochia* (22 species), *Ficus* (5 species in India besides the common fig), Araceae (26), *Amaranthus* (4), *Rawvolfia* (7), *Amorphophallus* (4), Araceae, *Heliotropium* (5, Heliotropiaceae), Asteraceae (*Eupatorium*, *Mikania*, *Vernonia*), *Terminalia* (5, Combretaceae), *Ipomoea* (6, Convolvulaceae), *Euphorbia* and *Phyllantus* (9 and 5, Euphorbiaceae), *Cassia* (6, Fabaceae), *Strychnos* (4, Loganiaceae), *Piper* (8, Piperaceae), *Zanthoxylum* (6, Rutaceae), *Solanum* (6, Solanaceae) and *Clerodendrum* (6, Verbenaceae). Also many ornamental or food plants are reported as having activity against snakebite: mango (*Mangifera indica*), litchi (*Litchi chinensis*), saffron (*Crocus sativus*), papaya (*Carica papaya*), chickpea (*Cicer arietinum*), nutmeg (*Myristica fragrans*), pepper (*Capsicum annuum*), longan (*Euphorbia longan*), castor (*Ricinus communis*), garlic and onion (*Allium cepa*, *A. sativum*), sweet potato (*Ipomoea batatas*), persimmon (*Diospyros kaki*), leaves of artichoke (*Cynara scolymus*), Brazilian oleander (*Nerium oleander*) in the Middle East, leaves of blood flower (*Asclepias curassavica*) in Central America, achiote (*Bixa orellana*) in India and the Philippines, roots of cassava (*Manihot esculenta*), the seeds of cacao (*Theobroma cacao*) in South America, coconut (*Cocos nucifera*), and many species in India such as sunflower (*Helianthus annuus*), pomegranate (*Punica granatum*), grape (*Vitis vinifera*) and cider (*Citrus medica*).

The following list of genera and species of South American plants have been reported as having antisnake activity:

Genus *Aloysia*

Aloysia citriodora Palau (Verbenaceae), syn. *Aloysia triphylla* (L'Hér.) Britton, syn. *A. citriodora* Ortega ex Pers., *hom. illeg., Lippia citriodora* (Lam.) Kunth. *comb. illeg., L. triphylla* (L'Hér.) Kuntze, *Verbena triphylla* L´Hér., *Zapania citriodora* Lam. is a very common species that grows in South America (Zuloaga and Morrone, 1999) (Cabrera, 1993).

Common Names

Lemon verbena, cedrón, hierba luisa (Jozamí and Muñoz, 1982); cerdón, cedrón de Castilla (Martínez Crovetto, 1961); in Brazil: salvia limao, erva cidreira (González Torres, 1997; Manfred, 1977).

Background

This species is widely used in ethnomedicine for preparation of teas or infusions with the leaves, flowers and young stems for treatment of a range of disorders including: indigestion, diarrhoea, vomiting, anxiety, nervous affections, hysteria (Cáceres, 1996), asthma, cough, fever (Bassols and Gurni, 1996). Leaf infusions are used as stimulant (Fester *et al.*, 1961); also as antimalarial, antineuralgic and tonic (Bassols and Gurni, 1996), (Gupta, 1995), (Toursarkissian, 1980); anti-inflammatory, analgesic, antipyretic, tonic and stimulant (Oliva *et al.*, 2010). Infusions were also reported as being antimicrobial and antimycotic (Sartoratto *et al.*, 2004; Oksay *et al.*, 2005); and antioxidant (Stashenko *et al.*, 2003). The essential oil is also used in perfumery and in the flavor industry for liquors and foods (Cáceres, 1996). In Argentina, the plant is an official drug in the Farmacopea Argentina and is included in the Código Alimentario Argentino. In Europe its use in perfumes is restricted because it was reported to be photo sensitizing (Bandoni, 2000). The plant is mentioned as having anti-venom activity only in a few reports, and these reports lack scientific evidence or confirmation of activity (Manfred, 1977; Duke *et al.*, 2009).

Chemical Constituents

The essential oil is composed mainly of: 1,8-cineole (15 per cent), limonene (1 per cent), a-pinene (0.5 per cent), citral a (37 per cent), citral b (22 per cent), geraniol (11 per cent), linalool (1 per cent) (Terblanché *et al.*, 1996); the essential oil of flowers (from Córdoba, Argentina): limonene (9 per cent), myrcene (2 per cent), a-pinene (1 per cent), a-thujone (17 per cent), mircenone (31 per cent), camphor (5 per cent), carvone (2 per cent), lippifoli-1(6)-en-5-one (africanone) (9 per cent) and spathulenol (3 per cent) (Zygadlo *et al.*, 1995). Neral (12 per cent), geranial (17 per cent), limonene (22-38 per cent) mainly *levo* isomer (98 per cent *l*-limonene and 2 per cent *d*-limonene) is found but is variable depending on stage of plant growth, as well as sabinene (6-15 per cent) mainly *dextro* isomer (99 per cent *d*-sabinene) and a sesquiterpene fraction (10-30 per cent) with caryophyllene, bicyclogermacrene and caryophyllene oxide and other compounds (Ricciardi *et al.*, 2011). Leaf infusions contain 400 mg/L verbascoside and 100 mg/L luteolin 7-diglucuronide; the same infusion yields 51 per cent of essential oil containing 77 per cent citral, far more than the citral content in leaves (41 per cent) (Carnat *et al.*, 1999).

Essential oil in plants from Brazil have: citral (59 per cent), geraniol (11 per cent), eucalyptol (15 per cent) and linalool (1 per cent); material from France: citral (38 per cent), geraniol (6 per cent), nerol (5 per cent), limonene (4 per cent); from Portugal: limonene (23 per cent) and citral (18 per cent) (Bandoni, 2000). The yield of essential oil of leaves and flowers from Guatemala representing 0.5–2 per cent (w/w) consisted of: cineol, citral (20–39 per cent), *l*-limonene (10–15 per cent), sesquiterpenes (β-caryopyhyllene, isocaryophyllene, 2,6-β-caryophyllene oxide) (40–45 per cent), linalool (3.5–11 per cent), *d*-verbenone, aldehydes and ketones (photocitral isomers, *l*-carvone, traces of furfural and kobusone) phenolic acids, acetic and valerianic acid, flavonoids, hydrolysable tannins, pyrrol, flavones and alkaloids (Cáceres, 1996).

Properties Tested

SDS-PAGE was done as part of an *in vitro* screening method to determine the anti-venom activity of all essential oils and extracts of aerial parts of the plant from three different geographical regions (Paso de la Patria, Laguna Brava and San Luis del Palmar, Corrientes, Argentina). The volatile samples showed a substantial modification of the electrophoretic profile of the venom of *B. diporus* which was evident by the disappearance of the phospholipases protein bands (18 kDa) (Camargo *et al.*, 2011). On the other hand, aqueous, alcohol or hexane extracts of aerial plant parts showed no activity by SDS-PAGE at the doses tested (Cáceres Wenzel *et al.*, 2012).

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Genus *Aristolochia*

Among species acknowledged as being useful against snakebite, and usually considered weeds, are those assigned with relative certainty to be in *Aristolochia*. Treatments for both internal and external use have been developed from material from different species and are well known to travellers who frequent areas with snake risk as well as naturalists.

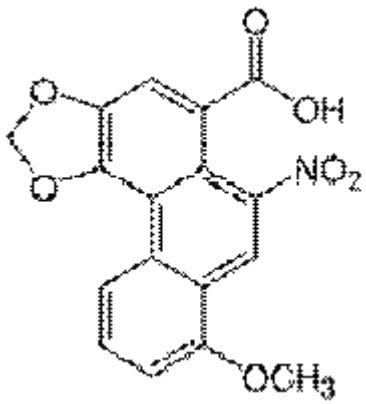
Background

- ☆ Bonpland and Azara: Prescribed treatments developed using materials from species of this genus have been considered in some cases to be unfailing in effectiveness against snakebite.
- ☆ Gonzalez Torres (1997): Recipes for mixtures of powdered root material for addition to beverage or wine or that can be applied directly in a compress for snakebites.
- ☆ *A. fimbriata* in infusions and compresses; *A. gibertii*; *A. labiosa*; *A. macroura* as antidote against cobra venom; *A. serpentaria* whose roots can act as snake repellent as well as having healing properties for snakebite and *A. triangularis* also acts against cobra bites (Ricciardi, 2005).

Chemical Constituents

Generally *Aristolochia* species are characterized by the presence of essential oil, but also presence of aristolochic acid (ACA), a phenanthrene-substituted carboxylic acid with ACA I, a nitroderivative. This compound is usually accompanied by aristolactams, or by germacranolides: aristolone, with ACA and *nor*aristolochic acid, in *A. clematitis*, whereas in *A. rotunda* and *A. longa*, aristolochic acid II (ACA II). Determination of ACAs is done by capillar electrophoresis (Priestap *et al.*, 2003; Ioset *et al.*, 2002).

Properties Tested



Aristolochic Acid

ACA inhibits inflammation and edema, is associated with relieving pain and functions as a non-competitive inhibitor of PLA2. ACA was found to form a weak 1: 1 complex with PLA2 resulting in an apparent increase in alpha helical secondary structure but with no measurable effect on tertiary structure (Vishwanath *et al.,* 1985; Vishwanath *et al.,* 1987a; Vishwanath *et al.,* 1987b; Vishwanath *et al.,* 1987c; Moreno, 1993; Houghton *et al.,* 1993; Pereira *et al.,* 1994 and 1992).

ACA was more recently found to have a high-affinity for PLA2 from *Vipera russelli* to provide a structural basis for inhibition of arachidonic acid biosynthesis leading to production of prostaglandins. The structure involved two crystallographically independent molecules of PLA2 as an asymmetric dimer with ACA bound specifically to only one of the two polypeptides, molecules A and B. ACA could bind to molecule A only while the binding site of molecule B is empty. Binding was associated with a change in conformational characteristics of W31 that resulted in a narrowing or occlusion of a hydrophobic channel serving as a passage to active site residues (Chandra *et al.,* 2002).

Toxicity

ACA is an irritant of mucus membranes and at high doses can cause respiratory paralysis. It is also nephrotoxic and carcinogenic (mutagenic). Oral administration or intraperitomeal injection of ACA to rats or mice resulted in stomach carcinomas and kidney fibrosis, and in rabbits a low incidence of renal tumors. Subcutaneous injection of ACA to rats caused urothelial kidney tumors and malignant fibrohistiocytic sarcomas at the site of injection. ACA I and II were shown to be mutagenic in several systems. A mixture of the two acids administered to rats was found to be so highly carcinogenic in a study in Germany that Aristolochiaceae plant materials were eliminated from homeopathic products.

ACA passed in maternal milk or increasing intravenous dosage of the acids can result in renal toxicity, nephrosis, renal failure and even death (DeSmet, 1995). These observations underscore the importance of only administering ACA topically. Persons most adversely affected (as nephropathologies) by ACA s were those known to have regular dietary supplements containing material from *Aristolochia* containing ACAs (IARC, 2002).

Aristolochia angustifolia, Cham. (Aristolochiaceae); syn. *A. angustifolia* Cham. var. *guaranitica* Ahumada (Martínez Crovetto, 1961)

Common Names

Cipo mil homens (González Tórres, 1997), luz del campo (Martínez Crovetto, 1961).

Aristolochia argentina Griseb. (Aristolochiaceae)

Common Name

Charruga (Domínguez, 1928)

Chemical Constituents

Essential oil is found throughout the whole plant with principal compounds: *cis* and *trans*-β-ocimene; linalool; (3*E*,5*Z*)-1,3,5-undecatriene; (*E*,*E*)-1,3,5-undecatriene; β-elemene; β-caryophyllene; (*E*)-β-farnesene; germacrene D; spathulenol, bicyclogermacrene (Priestap *et al.,* 2003b); lactams (Crohare *et al.,* 1974); seven aristolactams (Priestap, 1985a), two carboxyaristolactams and two hydroxymethyl aristolactams (Priestap, 1985b); specifically in roots: ARA, ARA I and II methyl esters (Priestap, 1982); other ARAs: (Priestap, 1987), argentilactone (Priestap *et al.,* 1977). Argentilactone is a mayor constituent of essential oil (57-89 per cent), and is allergenic as well as being a skin irritant. Plant extracts are also cytotoxic (Mongelli *et al.,* 2000).

Aristolochia elegans Mast. (Aristolochiaceae), syn. *A. hassleriana* Chodat; *A. littoralis* auct. (Parodi *et al.,* 1988).

Background

Used in Mexico against snake venoms. The species has anti-inflammatory activity like other *Aristolochia*, and inhibits phospholipases consistent with attenuating action of mediators of inflammation and pain (Hutt and Houghton, 1998). This species was also shown to have anticholinergic activity (Rastrelli *et al.,* 1997).

Chemical Constituents

In leaves, sesquiterpene hydrocarbons, β-caryophyllene, isocaryophllene and bicyclogermacrene, (in roots and stems) oxygenated sesquiterpenes: (*E*)-nerolidol (Vila *et al.,* 1997); *ent*-kaurane-16α,17-diol, (“)-cubebin, a-methylcubebin, methylcubebin, β-(“)-hinokinin, (“)-53-methoxyhinokinin, (“)-kobusin (Habib and El-Sebakhy, 1981).

Non-volatile compounds reported in leaves: (-)-(*R*,*R*)-7′-*O*-methylcuspidatin (El-Sebakhy and Waterman, 1994), aristololide, aristogin C and two porphyrins: aristophylls A and B (Wu *et al.,* 2000); diterpenoids as in the case of *ent*-16β,17-epoxykauran, *ent*-kaur-15-en-17-ol and *ent*-15β,16-epoxykauran-17-ol; pericampy linone-A, corydaldine, thalifoline, northalifoline, *N*-methylcorydaldine (El-Sebakhy *et al.,* 1989). In roots and stems: 4-methoxy-3, 42-oxydibenzoic acid, tetralones: aristelegone A, B, C and D; pericampylinone-A, E; (Wu *et al.,* 2000), lignans (Wu *et al.,* 2002); aristolactams and benzoyl alkaloids (Shi *et al.,* 2004); aristolochic acids, amides, aporphines, benzenoidsand steroids.

Properties Tested

Hexane and methanol extracts had anti-toxic activity against venom of Mexican scorpion *Centruroides limpidus limpidus* in rats, and *in vitro* inhibition of concentration-dependent venom induced contractions of ileum (Jiménez-Ferrer *et al.,* 2005).

Treatment of snakebite venom with aqueous and alcoholic extracts of leaves, roots and stems of plants from Corrientes, Argentina resulted in slight variations in the intensity of bands by SDS-PAGE electrophoresis, and did not affect hemolytic activity. The procoagulant activity was inhibited by alcoholic extracts of leaves (31 per cent, 1: 20) and roots (42 per cent, 1: 40). Alcoholic extracts of leaves (1: 120), stems (1: 120) and roots (1: 80) also inhibited casein proteolytic activity of *B. diporus* venom (Torres *et al.,* 2012).

Aristolochia eriantha (Aristolochiaceae)

Common Names

Cipo-mil-homens (González Torres, 1997)

Aristolochia fimbriata Cham. (Aristolochiaceae) syn. *A. ciliata* Hook, *A. ciliosa* Benth

Common Names

Patito, ipe-mí, flor de patito, pajarito (Iturralde, 1925).

Aristolochia gibertii Hook. (Aristolochiaceae)

Common Names

Ysypó mil hombres, contrayerba, ypemí, patito (Gonzalez Torres, 1997; Toursarkissian, 1980; Martinez Crovetto, 1961 Parodi, 1988).

Properties Tested

Methanol extracts showed enzymatic and non-enzymatic protection against lipid peroxidation in experiments using a free radical generating system on mice membranes (Velazquez *et al.,* 2003).

Alcohol (17 per cent) and aqueous (35 per cent) extracts of leaves inhibited procoagulant activity in *B. diporus* venom. Aqueous extracts of leaves were analyzed for ability to bind/inactivate this venom *in vitro* by SDS-PAGE. The extract caused the disappearance of two bands: 57.5 kDa (hemorrhagin NHFb, hemorrhagic metalloprotease) and 52.5 kDa. The intensities of other bands were greatly reduced, one of 28.2 kDa botroalternin (type C lectin inhibitor of thrombin) and botrocetin (platelet conglutinin) and 17 kDa (Phospholipase A2, myotoxin) (Torres *et al.,* 2004). Finally, extracts showed no inhibition of venom hemolytic activity, and alcohol extracts of: leaves (1: 150), stems (1: 150) and root (1: 100) inhibited casein proteolytic activity in B. diporus venom (Torres *et al.,* 2012a).

Aristolochia macroura Ortega (Aristolochiaceae); syn. *A. appendiculata* Vell, *A. caudata* Booth ex Lindl., *A. caudata* Parodi, *A. macroura* Gomez *var*. *subtrifida* Duchtr, *A. trilobata* Lindl.

Common Names

Nil hombres (Domínguez, 1928; Martinez Crovetto, 1961).

Background

Useful against cobra venom (Ahumada, 1978).

Aristolochia triangularis Cham. (Aristolochiaceae) syn. *A. antihysterica* Mart. ex Duch., *A. sellowiana* (Klotzsch) Duch., *A. paraguariensis* D. Parodi, *A. salpinx* Mast, *A. triangularis* Cham. *var. salpinx* (Mast.) Hauman.

Common Names

Mil hombres, ypemí, jarrinha, cipó cobra, papo-de-Peru (Gonzalez Torres, 1997; Toursarkissian, 1980; Dominguez, 1928; Parodi and Dimitri, 1988; Di Stasi *et al.,* 1989). ACA was found in roots.

Background

Commonly used against cobra bites (Oliveira Simoes *et al.,* 1998), and for the cytotoxic effects of this plant see Mongelli *et al*. (2000).

Aristolochia trilobata L.; (Aristolochiaceae)

Common Names

Jarrinha, mil hombres, papo de Peru, (Di Stasi *et al.,* 1989)

Genus *Asclepias*

Asclepias mellodora A. St.-Hil. (Asclepiadaceae), syn. *Asclepias campestris* Decne.

Common Names

Pasto de vibora, mboi ka'a (Dominguez, 1928; Gonzalez Torres, 1997; Toursarkissian, 1980; Ricciardi *et al.,* 1996; Amorin, 1988; Burkart, 1979; Marzocca, 1997).

Chemical Constituents

Desglucouzarin, the main cardanolide glycoside (Petricic, 1966); vincetoxin and asclepiadin (cardenolide), soluble in alcohol but sparingly soluble in ether; the glycoside yields asclepin after hydrolysis as a first derivative.

Background

The plant material is crushed or chewed to release active ingredients, and applied directly to snakebite wounds (Montenegro, 1711).

Properties Tested

Contains cardiotoxic cardenolides which inhibit myocardial Na^+/K^+ ATPase affecting conductivity and myocardial contractility. Alcohol extract of the aerial parts of *A. mellodora* inhibits proteolytic activity (Ricciardi Verrastro *et al.,* 2012).

Asclepias curassavica L.

The alcohol extract of leaves inhibits hemolytic activity of *B. diporus* venom *in vitro* (Torres *et al.,* 2007) and hexane extract of aerial parts inhibits the procoagulant activity (Torres *et al.,* 2008). Also, both alcoholic and hexanic extracts inhibit proteolytic activity of venom (Ricciardi Verrastro *et al.,* 2012).

Genus *Bidens*

Bidens pilosa L. (Asteraceae) annual grass of two recognized varieties: *B. pilosa* L. var. *minor* (Blume) Sherff and *B. pilosa* L. var *pilosa*, the latter having a greater geographic distribution. Syn.: *B. chilensis* DC, *B. hirsuta* Nutt., *B. pilosa* var. *minor* (Blume) Sherff., *B. pilosa* var. *radiata* Sch. Bip.

Chemical Constituents

Essential oil has limonene, borneol, germacrenes, cadinols, D-muurolol, 3-propyl-3-(2,4,5-trimethoxy) benzyloxy-pentan-2,4-dione, diterpenoids: phytol, phytylheptanoate, triterpenoids: squalene (Zulueta *et al.,* 1995), β-amyrin, lupeol, lupeylacetate, purines: caffeine and derivatives (Ogawa and Sashida, 1992); coumarins: esculetin; flavonoids: quercetin, isoquercitrin, luteolin, friedelin, friedelan 3-β-ol, (Geissberger and Sequin, 1991; Wang *et al.,* 1997), 5-*O*-methylhoslundin (Sarker *et al.,* 2000), steroids, stigmasterol (in leaves, Zulueta *et al.,* 1995), β-sitosterol, acetylenes: 2-*O*-β-D-glucosyl trideca-11-(*E*)-ene-3,5,7,9,-tetrain-1,2-diol (PA-1) (Pereira *et al.,* 1999), 2-β-D-glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne and 3-β-D-glucopyranosyloxy-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne (Ubillas *et al.,* 2000), β-D-glucopyranosyloxy-3-hydroxy-6-(*E*)-tetradecen-8,10,12-triyne (Alvarez *et al.,* 1996); phenylheptatriyne (Geissberger and Séquin, 1991); trideca-2,12-dien-4,6,8,10-tetrain-1-ol; trideca-3,11-dien-5,7,9-triine-1,2-diol; trideca-5-en-7,9,11-triine-3-ol; (Sarg *et al.,* 1991), in the root: 3,3'-dimethyl ether 7-*O*-α-*L*-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside and quercetin 3,3 '-dimethyl ether 7-*O*-β-D-glucopyranoside (Brandão *et al.,* 1998). Caffeine (Sarker *et al.,* 2000), acids: succinic, vanillic, capric, lauric, palmitic, palmitoleic, elaidic behenic, linoleic, linolenic, myristic, phytic; in leaves: elaidic and behenic acids (in leaves: Zulueta *et al.,* 1995); carotenoid pigments: xanthophyll; tannins (Chippaux *et al.,* 1997).

Properties Tested

Aerial parts are used for anti-venom treatments. The polyacetylenes (Alvarez *et al.,* 1996; Brandão *et al.,* 1997), linoleic and linolenic acids as well as flavonoids and friedelin and friedelan 3-ol are known to be anti-inflammatory (Geissberger and Séquin, 1991; Pereira *et al.,* 1999), plant extracts exhibit prostaglandin biosynthesis inhibitory activity (an inflammatory process) (Chippaux *et al.,* 1997). Intravenously and intraperitoneally treatment neutralizes the effect of Cameroon elapid snake, *Dendroaspis jameson*, venom, rich in neurotoxin agonists and antagonists of acetylcholine and whose toxicity is not dependent on the route of inoculation in rats. Such treatment also counteracts the action of other poisons and has anti-malarial activity (Oliveira *et al.,* 2004). The phenylheptatriyne is photoactive but unlike furanocoumarins, generates DNA crosslinks when UV irradiated (Wat *et al.,* 1979).

Genus *Baccharis*

Baccharis trimera (Less) DC (Asteraceae)

Common Names

Carqueja

Background

Used to treat liver ailments, rheumatism, diabetes as well as kidney, liver and digestive disorders. The active component is a neo-clerodane diterpenoid: 7a-hydroxy-3,13-clerodadiene-16,15: 18,19-diolide, $C_{20}H_{28}O_5$.

Properties Tested

Januário *et al*. (2004) observed that clerodane isolated from *B. trimera* inhibited hemorrhagic activity of *Bothrops* crude venom 70 per cent on fibrinogen in an approximate ratio 1: 10 w/w poison: clerodane. Also, metalloprotease activity, isolated from *B. jararacussú* venom, on casein at a ratio of 1: 10 protease/clerodane, was inhibited 80 per cent for Class I, and 89 per cent for Class II type metalloproteases. The strong hemolytic and proteolytic *Bothrops* venom inhibitory activity of clerodanes, as well as the beneficial effects on induced edema accompanying myotoxicity, indicates that continuing efforts to further develop snakebite treatments based on these natural products shows much promise as an alternative to treatment with heterologous serum.

Genus *Boerhavia*

Boerhavia diffusa L. var. *diffusa* (Nyctaginaceae), syn. *B. paniculata* Rich., *B. coccinea* var. *paniculata* (Rich.) Moscoso.

Common Names

Tangará (Gonzalez Torres, 1997), erva Tostao (in Brazil), in Venezuela, hierba de boca (Rodriguez, 1980).

Background

In some regions treatment against snake bite involves taking tea of leaves and roots and applying locally as a compress after cooking.

Boerhavia diffusa L. var. ***leiocarpa*** (Heimerl) Adams (Nyctaginaceae), syn. *B. paniculata* var. *leiocarpa* (Heimerl) Heimerl; *B. diffusa* var. *paniculata* D. Parodi, nom. nud.; *B. coccinea* var. *leiocarpa* (Heimerl) Standl.

Boerhavia repens L. (Nyctaginaceae), syn. *B. adscendens* Willd., *B. coccinea* Mill, *B. caribaea* Jacq., *B. diffusa* L., *B. paniculata* Rich. syn. *Boerhavia diffusa* L. var. *diffusa*.

Common Names

Tangará (Gonzalez Torres, 1997), in Venezuela, hierba de boca (Rodriguez, 1980), grows in tropical South America.

Genus *Brunfelsia*

Brunfelsia uniflora (Pohl) D. Don; (Solanaceae), syn. *Franciscea uniflora* Pohl.

Common Names

Jazmín del Paraguay, azucena, manacá, mercurio vegetal, Santa Maria. Half-height shrub, native to the Amazon, it is used as an ornamental because of its flowers.

Background

Used to treat snakebites in South America. The root has been used in Europe to treat snakebites.

Chemical Constituents

The essential oil consists of limonene, myrcene, ocimene, α-terpineol, terpinolene, geraniol, linalool, α-ionone, β-cyclocitral, β-bisabolene, elemol, nerolidol, farnesol, β-safranal, β-eudesmol, lavandulal, benzylbenzoate, isobutylsalicylate, benzylsalicylate, β-damascenone, 2-ethylfuran, *n*-heptane, *n*-octane, *n*-decane, *n*-pentadecane, *n*-heptadecane, *n*-hexadecane, *n*-nonadecane, *n*-pentacosane, heneicosane, tricosane, palmitic acid, myristic acid, linoleic acid, linolenic acid, pentadecanoic acid, neophytadiene (Maestri and Guzmán, 1995). Roots and bark have tropane alkaloids (lymphatic system stimulants) throughout the plant: mandragorine (central nervous system stimulant and anticholinergic) coumarins: esculetin, a furanocoumarin: scopoletin (analgesic and anti-inflammatory *in vitro*, induces psychopharmacological effects) (Ruppelt *et al.,* 1991), scopoline and other constituents: brunfelsene, lignans and sapogenins.

Properties Tested

Oral administration of plant infusions have been shown to have analgesic and anti-inflammatory activities (Ruppelt *et al.,* 1990).

Genus *Casearia*

Casearia sylvestris Sw (Flacourtiaceae) syn. *C. parviflora* Willd., *C. punctata* Spreng., *C. samyda* (Gaert) DC; *Samyda parviflora* L. *S. sylvestris* (Sw) Poir., *Anavinga samyda*.

Common Names

Burro kaá, cafe-bravo, cafeiillo, corta-lengua, guaçatonga. Background: Decoction of leaf applied topically and taken internally is used by natives of the Amazon and Bolivia for snakebite (Borges *et al.,* 2000; Raslan *et al.,* 2002).

Chemical Constituents

In leaves clerodane diterpenoids: casearvestrine A, B, and C, (Oberlies *et al.,* 2002); diterpenes: casearines G, S and T, (De Carvalho *et al.,* 1998; Morita *et al.,* 1991) and casearines A-F (Itokawa *et al.,* 1990); iridoids: 1-β-hydroxy-dihydrocornine; 1-α-hydroxy-dihydrocornine; α-gardiol; β-gardiol; plumericine; isoplumericine; 11-O-trans-caffeoylteucrein; ester derivatives: 2-methyl-4-hydroxy-butyl-caffeoate; 3-methyl-4-hydroxy-butyl-caffeoato; amides: N-[7-(3′,4′-methylenedioxyphenyl)-2Z,4Z-heptadienoyl] pyrrolidine and a triterpene: viburgenin. *Casearia* clerodanes I, II, III, IV, V and VI, polysaccharides and sterols sitosterol and stigmasterol, lapachol and saponins (Bolzani *et al.,* 1999).

Properties Tested

Tests done *in vitro* have shown the plant to have analgesic and anti-inflammatory properties (Ruppelt *et al.,* 1990). Aqueous extracts of leaves were able to: neutralize hemorrhagic activity form *B. asper*, *B. jararacussu*, *B. neuwiedi* and *B. pirajai*, as well as two metalloproteinases from *B. asper* and at various levels proteolytic activity on casein in venom of *B. neuwiedi*; partially protect α-fibrinogen from degradation by venom of *B. jararacussu*; reduce the increase in plasma clotting times caused by venom

of *B. jararacussu*, *B. moojeni* and *B. neuwiedi* (Borges *et al.,* 2001); inhibit Class I, II and III PLA_2 activity of various snake venoms, with having the greatest effect on Class II activity; inhibit myotoxic, anticoagulant and edema inducing activity in various venoms from *B. moojeni* and *B. jararacussu* (Borges *et al.,* 2000). Hydroalcoholic extracts of leaves or essential oil inhibits acute edema in mice caused by *B. alternatus*. Overall *C. sylvestris* is an excellent source of PLA_2 inhibitor, which is primarily responsible for the toxicity of lancehead venom. Plant extracts can counteract lethal doses of venom of vipers (mainly *Bothrops*) and bees.

Some *Casearia* have antitumor and cytotoxic activity (Itokawa *et al.,* 1988); anticancer activity, inhibit HIV replication or antibiotic activity on *Bacillus cereus* and *B. subtilis* (Itokawa *et al.,* 1990).

Casearia mariquitensis (Flacourtiaceae)

Aqueous extracts of leaves of *C. mariquitensis*, a plant found in Brazilian open pastures, neutralizes hematologic dysfunctions induced by the crude venom or by neuwiedase, 22 kDa class PI metalloproteinase from venom of South American *B. neuwiedi pauloensis*. Incubation of erythrocytes with venom and extract at a ratio of 1: 10 (w/w, venom/extract), was generally effective but did not affect the decrease in platelet levels induced by the venom. Plasma fibrinogen concentration decreased ca. 36 per cent and 83 per cent when 0.6 LD_{50} crude venom or neuwiedase, respectively, were i.p. injected in mice, and the aqueous extract could inhibit this effect. The beta fibrinogen chain was not degraded by crude venom or neuwiedase. The pulmonary hemorrhage induced by 0.6 LD_{50} i.v. injected neuwiedase was completely inhibited when pre-incubated with extract at a ratio of 1: 10 (w/w, toxin/extract) (Izidoro *et al.,* 2003).

Genus *Chaptalia*

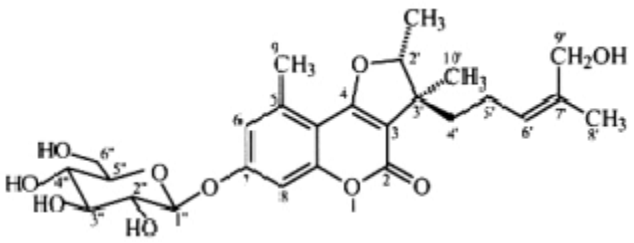
Chaptalia nutans (L.) Pol. (Asteraceae), syn. *C. nutans* (L.) Hemsl. comb. superfl., *C. subcordata* Greene, *Leria nutans* (L.) D.C., *Tusilago nutans* L.

Common Names

Peludilla, pelosilla, cerraja, lígua-de-vaca (Lemos de Arruga Camargo, 1999). Plant is found across north-central Argentina.

Chemical Constituents

The aerial parts: prunasin (*d* form of mandelonitrile glucoside), parasorbic acid, 5-methyl-3α-hydroxivalerolactone and coumarins: 4-*O*-β-glucopyranosyl-5-



7-*O*-β-D-glucopyranosyl-nutanocumarin

methylcoumarin. The roots: nutanocoumarin, 9'-*O*-β-glucopyranosyl-nutanocumarin, and 7-*O*-β-D-glucopyranosyl-nutanocumarin (Torrado Truiti *et al.*, 1998 and 2003).

Properties Tested

Aqueous extracts have anti-inflammatory activity comparable to indomethacin in carrageenan-induced models in *in vivo* tests using female rats (Badilla *et al.*, 1999).

Genus *Chiococca*

Chiococca alba (L.) C. L. Hitchc. (Rubiaceae), syn. *Ch. Brachiata* Ruiz and Pav., *Chiococca anguifuga*, Mart.

Common Names

Nianca (chiriguano, Bolivia), bejuco de barraco (Dominican Republic), cainca, cipo cruz, raíz fedorenta, caninana (Brazil), ysypo-kurusu, (Gonzalez Torres, 1997) grass withers, ka'aysá, ka'a-ysa, ysypo-kurusu, (Gonzalez Torres, 1997); Toursarkissian, (1980) brings *Ch. angifuga*, isipo curuzu, bejuco de verraco, cipó-cruz, "yianoa" (chiriguano, Bolivia).

Background

Effective against the venom of vipers (González Torres, 1997). In the Dominican Republic against snake bites and in Chaco (Argentina) the plant is known to be effective against poisons (De Luca and Zalles, 1992), indicated against cobra bite (Oliveira Simoes *et al.*, 1998).

Chemical Constituents

Pentacyclic triterpenoids, free or as glycosides of α-amyrin, β-amyrin (Bhattacharyya and Cunha, 1992), and oleanolic acid and ursolic ketoalcohols, lignans and coumarins (Abd El-Hafiz *et al.*, 1991), which would form a complex and would be responsible for the neutralizing the effects of snakebite. Methanol extract of roots: one C_{19} *nor*-seco-pimarane: merrilactone (Argaez Borges *et al.*, 2001).

Properties Tested

Analgesic and anti-inflammatory properties were found using *in vitro* tests (Ruppelt *et al.*, 1990).

Genus *Cissampelos*

Cissampelos glaberrima A. St.Hil. (Menispermaceae)

Common Names

Southern Brazil: South ka'apeva, jarrinha (Gonzalez Torres, 1997).

Chemical Constituents

Aporphynic alkaloids have been isolated from roots: cissaglaberrimine, trilobinine and a tricyclic lactone: eletefine (Barbosa-Filho, 1997).

Cissampelos pareira L. (Menispermaceae), syn. *C. pareira* L. var. *australis*; *Cissampelos pareira* L. var *australis* (A. St.-Hil-) Diels, *C. pareira* L. var *caapeba* var Eichler.

Domínguez also brings *C. pareira* var. *australis*, (St. Hil.), as a variety of *C. pareira* L. (Dominguez, 1928).

Common Names

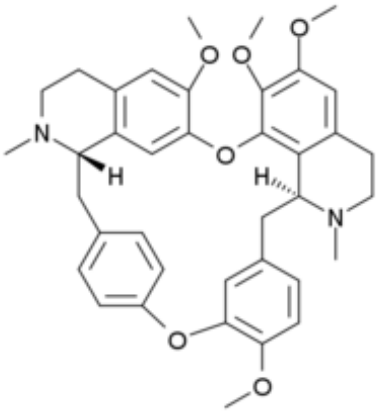
In Brazil this plant is well known as abutua, and in Peru as mullein. References to abuta in herbal commerce today, however, may refer to either *Cissampelos pariera* or an entirely different plant, *Abuta grandiflora*, another tropical vine containing different products and used for different purposes in South American herbal medicine. The confusion is because in Peru, *A. grandiflora* is called chiric sanago as well as abuta. In Brazil: ysypo cobra, parreira brava, abutúa (Gonzalez Torres, 1997), caá pebá, pareira brava, (Toursarkissian, 1980; Ricciardi *et al.*, 1996), mil hombres, pareira falsa, (Amorín, 1988), hoja de mono, butua, (Manfred, 1977), zarza, caá-pebá (Gupta, 1995), (Dimitri and Parodi, 1988), (Marzocca, 1997). Perennial, climbing with a woody base and climbing found throughout north central Argentina. Abuta is found throughout the Amazon in Peru, Brazil, Ecuador, and Colombia, and is cultivated by many to beautify gardens.

Background

Guatemala: Antidote, anti-rheumatic, cramps, diuretic, erysipelas, fever, menstrual disorders, snakebite, sweat promoter -Nicaragua: bites, fever, skin rash, sores, stings, venereal disease -Venzuela: bladder disorder, diuretic treatment, kidney stones, snakebite.

Chemical Constituents

Contains tetrandrine a bis-benzylisoquinoline alkaloid, reported as having analgesic, anti-inflammatory, fever reducing and cardioactive properties as well as hypotensive effects and also action against cancer and leukemia cells. Other isoquinoline alkaloids present are berberine (hypotensive antimicrobial), cissampeline, a skeletal muscle relaxant drug in Ecuador.



tetrandrine

In aerial parts: flavonoids (Ramirez *et al.*, 2003), leaves and roots contain alkaloids (Bhatnagar *et al.*, 1967a, Leger *et al.*, 2004; Basu, 1970); Bhatnagar *et al.*, 1967b; Kupchan *et al.*, 1965; Anwer *et al.*, 1968; Morita *et al.*, 1993; Morita *et al.*, 1995).

Properties Tested

Tetrandrine is the compound studied in greatest detail. The alkaloid has analgesic, anti-inflammatory and antipyretic properties. It also exhibits pareirubrine A and B activities; however tetrandrine is too toxic for use in humans. Berberine is also hypotensive, cisampelina is a smooth muscle relaxant, marketed as such (Farnsworth *et al.*, 1989), and palmatine has hypotensive and sedative activity. The anti-inflammatory activity of *C. pareira* can probably be attributed to the suppression of nitric oxide mediated inflammation by bis benzylisoquinolenic alkaloids (Kondo,

1993). Paste obtained from roots is used topically for fistules, pruritus, skin disorders and snake venom poisoning (Amresh *et al.,* 2003). The entire plant may be considered to have very potent anti-inflammatory activity, with ethanol extract of roots being a convenient way for collection and storage (Amresh *et al.,* 2007). Alcohol extract of leaves of species in northeastern Argentina completely inhibits hemolytic activity of venom from *B. diporus* (Torres *et al.,* 2007). Incubation of *B. diporus* venom with alcohol extract of the entire plant results in the disappearance of all protein bands including PLA_2 (ratio 1: 7 (venom: dried extract) by SDS-PAGE. Aqueous and alcohol extracts, however, did not affect venom coagulant activity (Sosa de Torres *et al.,* 2004).

Toxicity

C. pareira can be contraindicated for persons with low blood pressure. Tetrandine alkaloid present was documented to have various effects on heart function in animals and humans. Those with heart conditions or are taking heart medication should consult with a medical doctor before use of plant material.

Genus *Clematis*

Clematis bonariensis Juss. ex DC. (Ranunculaceae), syn.: *C. maldonadenses*

Common Names

Larranaga, cabello de angel, barba de viejo (Lahitte *et al.,* 1998).

Clematis montevidensis Spreng. (Ranunculaceae), syn.: *Clematis hilarii* Spreng, *C. denticulata* Spreng.

Common Names

Loconte, cabellos de angle, barba de viejo (Domínguez, 1928).

Chemical Constituents

In roots: ranunculin (protoanemonin glucoside with irritating action on skin), stigmasterol, 3-b-*O*-D-glucoside of stigmasterol, sitosterol and campesterol, and in aerial parts: *p*-hydroxycinnamic, oleanolic acid, campesterol, stigmasterol, sitosterol (Pettenati *et al.,* 2005).

Properties Tested

Infusion of the root and aerial parts of *C. montevidensis* showed a moderate diuretic activity in rats. This effect could be due, at least in part, to the levels of oleanolic acid present in this plant (Alvarez *et al.,* 2003).

Genus *Cyperus*

Cyperus obtusatus (J. and K. Presl) Mattf. and Kükenth. (Cyperaceae), syn.: *Kyllinga vaginata*, *K. pungens* Link. (Gonzalez Torres, 1997)

Background

Roots and leaves have aromatic calmative and antispasmodic activities, and that can neutralize properties of snake venom (Cabrera and Zardini, 1978), (Toursarkissian, 1980).

Cyperus sesquiflorus Mattf. and Kuek. (Cyperaceae) *Kyllinga odorata* Vahl syn.: *C. sesquiflorus* (Torr.) Mattf. and Kuk., *C. sesquiflorus* (Torr.) Mattf. and Kükenth. ex Kukenth., *K. sesquiflora* Torr. (Domínguez, 1928), (Matoso, 1983)

Common Names

Junco, jahapé, iasapé, capi-catí, capii catí, capim cheiroso, in Brazil: capim cedreira, esquinanto (Gonzalez Torres, 1997), capií catí, capim cheiroso (Toursarkissian, 1980; Ricciardi *et al.,* 1996).

Genus *Dorstenia*

Dorstenia brasiliensis Lam. (Moraceae), syn. *Dorstenia montevidensis* Miq.

Common Names

Contrayerba, taropé (guaraní), kaapiá, higuerilla, tiú-tiú, carapiá, caiapiá taropé, tayapiá (Gonzalez Torres, 1997), contrayerba, caapiá-assú, eiga-eiga, chupa-chupa, carapiá (Gupta, 1995; Olivera Simoes *et al.,* 1998; Toursarkissian, 1980; Domínguez, 1928; Matoso, 1893; Sorarú and Bandoni, 1978; Amorín, 1988; Ratera and Ratera, 1980).

Parts Used

Leaves in infusion, decoction of roots

Background

Digestive, emmenagogue, it has been widely used in the treatment of bites or stings from venomous animals or plant poisons. The roots of *Dorstenia brasiliensis*, have been used as a folk medicine for the treatment of digestive system disease and typhoid fever (Uchiyama *et al.,* 2002).

Chemical Constituents

In roots: triterpenoids; coumarins and furocumarins 7-hydroxycumarin (Cussans and Huckerby, 1975); marmin: psoralen, bergaptene, (Elgamal *et al.,* 1979) 22 -(13-hydroxy-13-metylethyl)-psoralen (Quader *et al.,* 1992) and bergaptene, in rhizomes: furanocumarin monoterpenoid: 5-[3-(4,5-dyhydro-5,5-dimethyl-4-oxo-2-furanyl)butoxy]-7H-furo[3-2-g][1]benzopyran-7-one, 5-[[3-(4,5-dyhydro -5,5-dimethyl-4-oxo-2-furanyl-2-butenyl-oxy]-7H-furo[3-2-g][1]benzopyran-7-one (Kuster *et al.,* 1994); (22*S*, 32*R*)-32-hydroxymarmesin (Vilegas and Pozetti *et al.,* 1993); glycosides of hydroxymarmesin, (22*S*, 32 *R*) – hydroxymarmesin, 42-O-b-D-glucopy ranoside; glucosides of hydroxymarmesin (22*S*,32*R*)-32-hydroxymarmesin, 42-*O*-β-D-glucopyranoside; (Lemmich *et al.,* 1983); (22*S*,32*R*)-32-hydroxymarmesin 42-*O*-β-D-glucopyranoside; (22*S*)-marmesin 42-*O*-α-L- rhamnopyranosyl (1→6)-*O*-β-D-glucopyra noside (Srivastava and Srivastava, 1993); phenoline (probably responsible for the anti-venom activity); in roots: two 3,4-seco-adianane-type triterpenoids (Uchiyama *et al.,* 2002), sterols: sitosterol, stigmasterol, 3-*O*-β-glucosylsitosterol (Kuster *et al.,* 1994).

Properties Tested

The furanocoumarins or psoralens are photosensitizers that can cause genetic damage and burns from exposure to UV radiation. *In vitro* testing has shown these

compounds have analgesic and anti-inflammatory properties (Ruppelt *et al.,* 1991). Alcohol extracts of roots inhibit procoagulant activity of *B. diporus* venom (Torres *et al.,* 2008).

Dorstenia tenuis Bonpl. ex Bureau, (Moraceae), contrayerba, taropé. (Gonzalez Torres, 1997), (Sorarú and Bandoni, 1978; Matoso, 1893).

Dorstenia tubicina Ruiz and Pav. (Moraceae), syn.: *D. tubicina* f. *subexcentrica* Hassl.; *D. tubicina* var. *opifera* (Mart.) Hassl., caá-apiá, cayá-piá, carapiá (Brazil), contra-yerba (Peru).

Echium vulgare L. (Boraginaceae), snake tounge, (Manfred, 1977) Pyrrolizidine alkaloids have an accumulative toxicity in the liver.

Genus *Eclipta*

Eclipta prostrata (L.) L. (Asteraceae), syn. *Eclipta alba* (L.) Hassk., *Cotula alba* L., *C. prostrata* L., *E. brachypoda* Michx., *E. erecta* L., *E. longifolia* DC., *E. parvifolia* DC., *E. procumbens* Michx., *E. prostrata* L., *E. thermalis* DC., *E. zipeliana* DC., *Micrelium asteroides* Forsk., *M. tolak* Forsk., *Verbesina alba* L., *V. conysoides* Trew., *V. prostrata* L.

Common Names

Eclipta, hesillo, tangará-ka'á (Gonzalez Torres, 1997; Domínguez, 1928). It is an ascending, erect, ramifying, invasive annual grass in paddy fields, found throughout the northcentral part of the country.

Background

This plant is used against snakebite in Paraguay by Amazonian Indians (Marzocca, 1997), who may also take infusions as a preventative mesure against possible bite by venomous snakes (Mors *et al.,* 1989).

Chemical Constituents

Contains wedelolactone, dimethylwedelolactone; eclalbasaponins I-VI; taraxastone glucosides of: eclalbasaponins VII, VIII, IX and X (Yahara *et al.,* 1997) and a triterpenoid glucoside, ecliptasaponin C (28-*O*-β-D-glucopyranoside of the 3-β-*O*-β-D-glucopyranosyl-19-β-hydroxy olean-12-ene-28-oic acid) (Zhang and Chen, 1996; Zhang and Guo, 2001), daucosterol and 3-*O*-glucoside of the estigmasterol.

Properties Tested

Wedelolactone, estigmasterol and sitosterol act synergistically *in vitro* to neutralize the myotoxicity and hemorrhagic effect of a number of Crotalid venoms including those of *B. jararaca*, *B. jararacussu* and *Lachesis muta*. The activities implicated are anti-proteolytic, anti-PLA_2 and therefore anti-inflammatory (Melo *et al.,* 1994). Methanol extract of aerial parts of *E. prostrata* neutralize the letal activity of South American rattlesnake venom (Mors *et al.,* 1989; Melo *et al.,* 1994; Martz, 1992; Houghton and Osibogun, 1993; Melo and Ownby, 1999). Butanol extract, the major component being dimethylwedelolactone, neutralize the lethal hemorrhagic, proteolytic and PLA_2 activity of the Malayan pit viper (*Calloselasma rhodostoma*) (Pithayanukulo *et al.,* 2004).

Hexane extract of aerial parts inhibits procoagulant and haemolytic activity of *B. diporus* venom (Torres *et al.*, 2007 and 2008).

Genus *Erythrina*

Erythrina crista-galli, L. (Fabaceae-papilionoideae),

Common Names

Ceibo, zuinandí, ivirá-iputezú

Chemical Constituents

Erythrina alkaloids: erisovine, erisopine, erisodine, erisovine, eritramine, eritraline and eritratine have strong anesthetic and neuromuscular blocking activities.

Erythrina dominguezii Hassl., Chacho seibo, seibo rosa, in northeast Argentina

Erythrina falcata Benth., ceibo, suinana

Genus *Eupatorium*

Eupatorium ayapana Veuten (Asteraceae), syn. *E. oblongifolium* (Spreng.), Baker, *E. triplinerve*, *Conyza oblongifolia* Spreng.

Common Names

In Brazil: yerba de serpiente, iapana, diapana, guaco (Di Stasi *et al.*, 1989; Manfred, 1977), ajapá, yerba de lagarto.

Eupatorium oblongifolium (Spreng.) Baker, (Asteraceae), syn. *Conyza oblongifolia* Spreng.

Common Names

In Brazil: ajapa (Gonzalez Torres, 1997)

Background

In Paraguay infusions of the plant are used at a dilution of 20-30/1000 for treatment of snakebite (González Torres, 1997)

Species of this genus have essential oils containing terpenes, sesquiterpenes (Maia *et al.*, 2002).

Genus *Euphorbia*

Euphorbia dichotoma Forsk, (Euphorbiaceae)

Common Names

Mbói-ka'á, yerba del colmillo, solimán de la tierra (Gonzalez Torres, 1997).

Euphorbia hirta L. (Euphorbiaceae) syn. *Chamaesyce hirta* (L.) Millsp

Common Names

Hierba de la víbora (Gonzalez Torres, 1997), ka'á-ysy-guasú, (Parodi and Dimitri, 1988), erva de sapo, tupasy camby (Marzocca, 1997; Manfred, 1977; Domínguez, 1928).

Chemical Constituents

The ellagitannins, euphorbine A and B, are probably responsible of the anti-venom activity much like the triterpenoids, taraxerol and α- and β-amirin. Polyphenols that have been identified in leaves include: galic acid, quercitrin, myricetrin, 3,4-di-*O*-galloylquinic acid, 22,4,6-tri-*O*-galloyl-*D*-glucose,and 1,2,3,4,6-penta-*O*-galloyl-ß-*D*-glucose (Chen, 1991; Galvez *et al.,* 1993a; Galvez *et al.,* 1993b); in the milky sap there are diterpenoid esters that are irritating to eyes and skin. The flavonoid rutin (= 3-*O*-rutinoside of quercetin) is likely responsable for the anti-venom activity.

Properties Tested

Extracts of leaves were found to increase excretion of urine and eletrolytes in rats (Johnson *et al.,* 1999).

Euphorbia hypericifolia L. (Euphorbiaceae)

Common Names

hierba de la víbora (Gonzalez Torres, 1997), mbói-ka'á, yerba del colmillo de la víbora, solimán de la tierra (Gonzalez Torres, 1997)

Euphorbia serpens Kuntze (Euphorbiaceae), syn. *Euphorbia serpens* Kuntz. var. *microphylla* Müll. Arg. Cab. A perennial prostrate herb distributed widely throughout Argentina found in two varieties: *E. serpens* Kunth. var. *microphylla* Müll. Arg. and *E. serpens* Kunth. var. *serpens*.

Common Names

Hierba de la víbora (Gonzalez Torres, 1997), yerba meona, yerba de la golondrina (Toursarkissian, 1980; Amorín, 1988), ka'á-kambý, caá ambuy, in Paraguay (Domínguez, 1928; Gupta, 1995; Marzocca, 1997).

Background

The plant is known as yerba meona because of it diuretic activity.

Chemical Constituents

Lanosterol, quercetin, salicylic acid and the alcohol cycloartenol:

Genus *Fevillea*

Fevillea trilobata L. (Cucurbitaceae), syn. *F. cordifolia* Vell.

Common Names

Andirova, ñandyrová, Cipó de jabotí, haba de San Ignacio (Domínguez, 1928; Manfred, 1977; Gonzalez Torres, 1997).

Background

Scraped or ground seeds or oil of the seeds have anti-venom activity against snakebite (Rodriguez, 1980).

Chemical Constituents

Methanol, aqueous or alcohol seeds extracts contains: fevicordin A glucoside, fevicordin F gentiobioside, cayaponoside B, cayaponoside D, norcucurbitacinic

glycosides: andirobicine A glucoside, andirobicine A gentiobioside, andirobicine B glucoside, andirobicine C gentiobioside; (Valente *et al.*, 1993; Valente *et al.*, 1994).

Genus *Flaveria*

Flaveria bidentis (L.) Kuntze, (Asteraceae), syn. *F. bonariensis* D.C.; *F. contrayerba* (Cav.) Pers., *Ethulia bidentis* L., *Milleria chiloensis* Hort., *M. contrayerba* Cav.,

Common Names

Carapiá, ka'apiá, pique, chasca, (Gonzalez Torres, 1997; Toursarkissian, 1980), matagusanos, fique, flor amarilla (Amorín, 1988), balda, chasca, (Domínguez, 1928; Ratera and Ratera, 1980).

Background

The plant constitutes a popular remedy for both internal and external use against snakebite (Gonzalez Torres, 1997; Sorarú and Bandoni, 1978; Lartigue, 1971).

Chemical Constituents

This species is characterized by having flavonoid sulfates: 3,7-isorhamnetin disulfate (Cabrera and Juliani, 1976, 1977 and 1979) 3,7,32-quercetin trisulfate (Cabrera *et al.*, 1985); the 7,3′,4′-trisulfate of 3-acetyl quercetin and the 3,7,3′,4′-tetrasulfate of quercetin (Pereyra de Santiago and Juliani, 1972). These quercetin sulfates have been demonstrated *in vitro* to affect anti-thrombotic and anti-coagulant activity by increasing the partial time of thromboplastin activated (Guglielmone *et al.*, 2002); in roots and aerial parts: α-terthienyl and 5-(1-buten-1-inyl)-2,2′-bithienyl (Agnese *et al.*, 1999).

Genus *Ipomoea*

Ipomoea indica (Burr. f.) Merr, (Convolvulaceae), syn. *I. acuminata* auct. non (Vahl.) Roem. and Schult.

Common Names

Bejuco, suspiro, campanilla (Cabrera, 1993)

Background

Anti-venom (Marzocca, 1997; Hieronymus, 1882), some species have alkaloid derivatives of lysergic acid and ergoline.

Genus *Iresine*

Iresine diffusa Humb. and Bonpl. ex Willd. var. *diffusa*, (Amaranthaceae), syn. *I. celosioides* L., *Iresine celosioides* L. (Domínguez, 1928)

Common Names

Mbói-ka'á, yerba del colmillo de la víbora, solimán de la tierra (Gonzalez Torres, 1997).

Chemical Constituents

Compounds identified in aerial parts from this genus: drimenes: 3β,14-dihydroxy-δ(7,8)-drimen-11,12-acetonide, 3β,7β,14-trihydroxy-δ(8,9)-drimen-11, 12-olide and 3β,7α,14-trihydroxy-δ(8, 9)-drimen-11,12-olide (Rios and Berber, 2005).

Properties Tested

Alcohol extract of aeral parts inhibits procoagulant activity of *B. diporus* venom (Torres *et al.,* 2008).

Genus *Kyllinga*

Kyllinga odorata Vahl, (Cyperaceae); syn. *Cyperus sesquiflorus* Torr. (Mattf. and Kük.) ex and Kük.

Common Names

Capií catí, esquinanto, esquinanto menor, jahapé, iasapé, cortadera, capim cedreira.

Background

Roots and leaves are considered to have viper poison neutralizing properties (Gonzalez Torres, 1997).

Chemical Constituents

Composition of the essential oil of roots depends on the plant's origin, and sesquiterpenoids have been identified for the most part, including: β-pinene, camphene, 1,8-cineole, *p*-cymene, limonene, δ-cadinene, cadalene, γ-calacorene, *trans*-calamenene, α-copaene, copadiene, cipera-2,4-diene, cipera-2,4(15)-diene, ciperorotundene, epoxyguaiene, γ-gurjunene, α-muurolene, γ-muurolene, nootkatene, α-selinene, *epi*-α-selinene, β-selinene, selinatriene, rotundene, (-) *nor*-rotundene, (-) *iso*rotundene, patchoulene, valencene, ylanga-2,4-diene, ciperol, isociperol, α-rotunol, β-rotunol, rotundenol, 4α,5α-osidoeudesm-11-en-3α-ol,α-ciperon, β-ciperon, ciperenon, ciperolon, ciperadion, ciperorotundon, kobudson, isokobuson, muskaton, patchoulenon, rotundon, (Sonwa and König, 2001), 4,5-secoeudesmanolid and epimer and cyclic acetal, (Ohira *et al.,* 1998), oleic, linoleic, linolenic, oleanolic and myristic acid.

Genus *Laennecio*

Laennecio sophiifolia (Kunth.) G. L. Nesom, (Asteraceae), syn. *Conyza serpentaria* Griseb.

Common Names

Hierba del zorro, hierba de la serpiente (Hieronymus, 1882)

Chemical Constituents

In aerial parts compounds identified include: 2β- hydroxyhardwickiic acid (Jolad *et al.,* 1988), hautriwaic acid, (Hsü *et al.,* 1971), apigenine, β-sitosterol, 12-*epi*-bacchotricuneatin A (Simirgiotis *et al.,* 2000)

Properties Tested

Components of aerial parts extracted with non-polar solvent were shown to have strong anti-inflammatory effects after injection into mice (Cifuente *et al.*, 2001).

Genus *Macfadyena*

Macfadyena unguis-cati (L.) A. H. Gentry, (Bignoniaceae), syn.: *Bignonia unguis-cati* L.

Common Names

Uña de gato, teyú isipó, mbaracayá poapé (Lahitte *et al.*, 1998).

Background

The decoction of bark provides an antidote for snakebite (Lahitte *et al.*, 1998); the aerial parts are generally considered to have anti-inflammatory, anti-malarial and anti-venom properties (Duarte *et al.*, 2000).

Chemical Constituents

Corimbside, vicenin-2, quercitrin, chlorogenic and isochlorogenic acids, lupeol, β-sitosterol, β-sitosterylglucoside, alantoin and lapachol (Duarte *et al.*, 2000).

Genus *Mimosa*

Mimosa *pudica* L. (Fabaceae, Mimosoideae); syn. *Mimosa tetrandra* Humb.& Bonpl. ex Willd.

Common Names

Mimosa, sensitiva, dormidera, malicia de mujer.

Background

Infusions of roots are used for treatment of snakebite in Paraguay (Gonzalez Torres, 1997).

Chemical Constituents

Identified in aerial parts: β-[*N*-(3-hydroxy-4-pyridone)]-α-amino propionic acid (Kleipool and Wibaut, 1950; Tiwari and Spencer, 1965; Tiwari *et al.*, 1967), crocetin, *p*-coumaric acid (*p*-hydroxycinnamic acid); 7,32 ,42-trihydroxy-3,8-dimethoxyflavone; 7,32,42-triacetoxy-3,8-dimethoxyflavone (Kirk *et al.*, 2003; Lobstein *et al.*, 2002). Two rare C-glycosylflavones (43-hydroxymaisin and cassiaoccidentalin B) were isolated from plant material from Africa (Englert *et al.*, 1994) that was not found in American material. Other researchers found sitosterol (Jiang *et al.*, 1990) and a bufadienolid (Yadava and Yadav, 2001).

Properties Tested

Aqueous extract of roots, at specific doses, inhibits activity of hyaluronidase and protease in venom of Indian snakes (*Naja naja*, *Vipera russellii* and *Echis carinatus*) (Girish *et al.*, 2004). The aqueous extract of dried root also exhibits a significant effect on reversing lethality, myotoxicity and toxic enzyme activity in venom of cobra *N. kaouthia*, however this activity was absent in alcohol extracts (Mahanta and Mukherjee, 2001).

Genus *Mikania*

Mikania cordifolia (L.f.) Willd. (Asteraceae), syn. *Cacalia cordifolia* L.f., *Willoughbya cordifolia* (L.f.) O. Kuntze

Common Names

Guaco rebalsero, guaco verde (Rodríguez, 1980; Martínez Crovetto, 1981; Iturralde, 1925)

Chemical Constituents

Alcohol extract of leaves can be fractionated on a column using a mixture of solvents with increasing polarity (hexane, ethyl acetate, methanol), in which saponins elute first and were separated from alkaloids in subsequent fractions (Camargo *et al.,* 2010).

Properties Tested

Butanol extracts of leaves of *M. cordifolia* demonstrated strong *in vitro* activity against *Trypanosoma cruzi* and *Trichomonas vaginalis* (Muelas Serrano *et al.,* 2000). In addition, a number of other pharmacological activities were found including: anti-fungal, anti-microbial, bronchodilatory, anti-allergic, and particularly snake venom specific anti-inflammatory activity.

Alcohol extract of aerial parts and roots and hexane extract of roots of *M. periplocifolia*, alcohol and hexane extracts of aerial parts as well as those of roots of *M. micrantha* and alcohol extracts of aerial parts and alcohol and hexane extracts of root of *M. coridifolia* showed inhibitory activity *in vitro* against the proteolytic activity of *B. diporus* venom (Torres *et al.,* 2010).

Mikania micrantha H.B.K. (Asteraceae),

Common Names

Guaco (Toursarkissian, 1980).

Mikania periplocifolia **Hook. *et* Arn**. (Asteraceae), syn. *M. scandens* Willd. var. *periplocifolia* (Hook *et* Arn.) Baker

Common Names

Guaco (Toursarkissian, 1980; Amorín, 1988)

Background

After cooking the plant, it is useful against the bites/stings of snakes and insects (Valeta, 1935).

Chemical Constituents

The genus *Mikania* is characterized by the presence of alkaloids, lactones and sesquiterpenes like mikanolide, dihydromikanolide, deoxy-mikanolide, miscandenin, some with toxicity and being carcinogenic (Ricciardi, 2005).

Hexane extract of aerial parts and roots, alcohol extract of roots and essential oils of *M. coridifolia*; hexane extract of aerial parts and aqueous extract of roots of *M.*

micrantha and hexane extract of aerial parts of *M. periplocifolia* inhibit procoagulant activity of *B. diporus* venom (Torres *et al.,* 2008). Aqueous extract of aerial parts and roots of *M. micrantha* indirectly inhibits *B. diporus* venom hemolytic activity (Torres *et al.,* 2007).

Genus *Morrenia*

Morrenia odorata (Hook. and Arn.) Lindl, (Asclepiadaceae), syn.: *Cynanchum odoratum* Hook. and Arn.,

Common Names

Tasi, isipó (Martínez Crovetto, 1981); tasi, doca, (Domínguez, 1928), leche-leche, uruma**,** tasi, doca, (Parodi and Dimitri, 1988), tasi fragante, guaicurú rembiú, isipó a, tasi, doca, (Marzocca, 1997)

Background

The thin woody vines can be used as part of medical devices such as for tubal ligations (Martínez Crovetto, 1961).

Genus *Nectandra*

Nectandra angustifolia (Schrad.) Nees and Mart. ex Nees. (Lauraceae), syn.: *N. angustiflora* var. *falcifolia* Nees.; *N. falcifolia* (Nees) J.A. Castigl. (Parodi and Dimitri, 1988) ex Mart. Crov. and Piccinini; *N. membranacea var. falcifolia* (Nees.) Hassl.*; Ocotea angustifolia* Schrad.

Common Names

Ajuí, ajuý or laurel (Gonzalez Torres, 1997) laurel amarillo, aju'y hû, laurel-hu, laurel del río, laurel mini (Bertucci *et al.,* 2008), louro-branco (Marques, 2001). The seeds of *Nectandra sp*. acquired the name *Ishpingo* in colonial period of the 16th century, but are now referred as *hamalas* (Carod-Artal and Vazquez Cabrera, 2007).

Background

Leaf infusión of *N. angustifolia* (Lauraceae) are used in folk medicine for digestion (Martinez Crovetto, 1961), for treatment of rheumatism, arthritis and pain (Bertucci *et al.,* 2008), for digestion and for anti-venom properties against sting/bite of snakes (Gonzalez Torres, 1997).

Chemical Constituents

Essential oils of aromatic species were studied for the first time by Fester *et al*. (Fester *et al.,* 1961). Plant material for study was from Alto Verde and Puerto Ocampo (Santa Fe, Argentina). The terpenes identified were: α-pinene, 1,8-cineole and safrole; later Torres *et al*. (2005) determined the composition of essential oils in samples from San Isidro (Corrientes): α-pinene; β-pinene; β-myrceno; α-phellandrene; *p*-mentha-1(7),8-diene; limonene; (*E*) β-ocimene; γ-terpinene; α-terpinolene; δ-elemene; β-elemene; aromadendrene; germacrene D; bicyclogermacrene and α-chamigrene.

This species is stable with respect to expression of secondary metabolites, evaluated by production of volatiles, without significant variation in composition in

different vegetative states in that essential oils in fall, spring and summer were consistently characterized by high levels of terpene hydrocarbons: 69.4 per cent, 72.2 per cent and 63.6 per cent, respectively. Variation in specific compounds was, respectively: *p*-1(7),8-menthadiene (25.4 per cent 25.2 per cent and 24.7 per cent), α-terpinolene (18.8 per cent, 20.9 per cent and 3.3 per cent), α-pinene (8.8 per cent, 10 per cent and 13.4 per cent) and β-pinene (2.8 per cent 3.7 per cent and 5.2 per cent). The very small oxygenated fraction contained: oxygenated monoterpenes (0.2 per cent, 0.4 per cent and 11.7 per cent) and oxygenated sesquiterpenes (4.3 per cent, 4.5 per cent and 8.4 per cent). Other compounds found in this fraction included (*E*)-asarone, which has proven analgesic activity. The sesquiterpene hydrocarbon fraction (21.1 per cent, 19.8 per cent and 12.8 per cent respectively) was primarily represented by germacrene D (6 per cent, 5.2 per cent and 1.3 per cent). Enantiomeric relations found were: α-pinene 83 per cent (1*R*,5*R*)-(+) and 17 per cent (1*S*,5*S*)-("); β-pinene 80 per cent (1*R*,5*R*)-(+), 20 per cent (1*S*,5*S*)-(-) and limoneno 44 per cent (4*R*)-(+) 56(4*S*)-(-) (Torres *et al.*, 2011; Torres, 2011).

Alcohol extracts (EtOH: H_2O 70: 30) of leaves of *N. angustifolia* were found to have triterpenes/steroids, flavonoids and glycosides; in acetone extracts: triterpenes/steroids, low molecular weight terpenes and flavonoids and in chloroform extracts: triterpenes/steroids, low molecular weight terpenes and alkaloids (Bertucci *et al.*, 2008)

Separation by flash chromatography using solvent mixtures of increasing polarity (hexane, ethyl acetate, methanol) allowed for identification of flavonoids in fractions 2, 4 and 8; saponins in 2, 3, 4, 8 and 9; triterpenes/steroids in fraction 4, phenols in fractions 4 and 8 and alkaloids in 6, 7 and 8 (Torres *et al.*, 2010b).

Properties Tested

Truiti (2004) showed that *N. angustifolia* leaf crude extract reduced capillary permeability inflammatory activity caused by inducing agents. In 2005, the same author demonstrated this activity in a carrageenan-induced pleurisy model in which leaf ethanol extract was administered orally (nasogastric tube). Anti-inflammatory activity of leaf crude extract was also examined by Oliveira de Melo *et al*. (2006). They showed that the extract caused a reduction in intensity of rat paw edema response 2 and 4 h after injection of carrageenan inducer. Nasogastic administration of crude extract to rats reduced levels of pleural inflammatory effusion induced by carrageenan and without altering the number of leukocytes. The total nitrates concentration (NO_3^- + NO_2^-) in the induced pleural effusion was not different with *N. falcifolia* extract treatment.

Plant extracts were also effective in inhibiting trasudation of liquid and chemotactic influx of cells by *Croton* oil-induced edema on mice ears. This was also indicated by reduction in activity of the enzyme myeloperoxidase. Biological trials of ethanol extracts from leaves of *N. falcifolia* collected near the shores of the Upper Paraná River had antiprotozoal and molluscicidal activities (Truiti *et al.*, 2005). These extracts showed antileishmaniasic activity with an LD_{50} of 138.5 µg/mL for promastigote form of *Leishmania* (Viannia) *braziliensis* and 65.6 ± 5.4 per cent growth

inhibition at a higher dose of 320 µg/mL. The inhibition of the growth of epimastigote of *Trypanosoma cruzi* requires concentrations in the range of 1000 µg/mL.

Camargo *et al*. (2005) showed ethanol extracts of leaves to have concentration-dependent *in vitro* anti-hemolytic activity against venom of *B. neuwiedi diporus.*

Torres *et al*. (2011b and 2010) found that alcohol extracts of leaves had the highest *in vitro B. diporus* anti-venom activity. In addition, this activity had higher levels of anti-coagulant activity when isolated from plants in autumn and spring (Torres *et al.,* 2008), and highest hemolytic activity when isolated in spring (Torres *et al.,* 2007). There were also no differences in proteolytic activity isolated from plant material from different stages of vegetative growth (Torres *et al.,* 2010b). These results indicate that the plant must be harvested in springtime for preparation of alcohol leaf extracts. Alcohol and hexane extracts of leaves inhibit proteolytic acitivity in *B. diporus* venom (Torres *et al.,* 2010).

In *in vivo* tests, this active fraction was not toxic and provided protection (ED_{50}) from the lethal action ($4LD_{50}$) of venom injected intraperitoneally in experimental mice (Torres *et al.,* 2012b).

Flash chromatography was used to fractionate venom extract using (SDS-PAGE) to test for activity. Sub-fraction 5 was found to be the most effective in reducing intensity or completely eradicating bands present in venom after preincubation of venom and subfraction in a 1: 2 ratio (venom-subfraction). Chemical analysis indicated presence of phenols in this active subfraction, and further separation of this fraction by HPLC-DAD showed the presence of five components, all with a UV absorption spectrum typical of flavonoids (Torres *et al.,* 2010b and 2011b).

Leaf essential oils in aqueous distillates of plant material collected in autumn or spring exhibited high levels of inhibition against coagulation activity in venom of *B. diporus*.This activity was greater than that from essential oil aqueous distillates obtained in summer. None of the essential oils had hemolytic activity in *in vitro* test. Inhibition of proteolytic action in *B. diporus* venom by both essential oils as well as extracts of aqueous distillates was found using a venom-mediated casein proteolysis assay, but large venom: extract ratios (>1: 300) were necessary to measure this activity (Torres *et al.,* 2011c).

Nectandra megapotamica (Spreng.) Mez. syn.: *Nectandra membranacea* (Spreng.) Hassl., hom. illeg.*; N. membranacea var. saligna* (*Nees* and Mart. ex Nees) Hassl.*; N. membranacea var. saligna floribunda* Hassl.*; N. saligna* Nees and Mart. ex Nees*; N. saligna var. obscura* Meisn.*; N. tweediei* (Meissn.) Mez.*; Oreodaphne tweediei* Meisn.; *Tetranthera megapotamica* Spreng.

Common Names

Canela preta (Ilza and Naría, 2000), laurel hu, canela imbuia, canela-fedorenta, ayuí-hú, laurel negro, laurel hú, laurel canela, laurel amarillo, canela negra, laurel, ayuy morotí, ayuy pará, laurel ayuy, laurel blanco, laurel overo (Richter and Dallwitz, 2008). Canela-preta, Canela-so-mato (Da Silva Filho *et al.,* 2004b), canelinha (Melo *et al.,* 2004a) canela-amarela (Marqués, 2001).

Chemical Constituents

Psychoactive compounds were reported in seeds of *hamala* (Carod-Artal and Vazquez Cabrera, 2007). Da Silva Filho *et al*. (2004a) isolated three main components from hydroalcoholic crude extracts of *N. megapotamica*: α-asarone, galgravin and veraguensin. These compounds have analgesic and anti-inflammatory activities in mouse models with α-asarone being the main component responsible for the analgesic effect. The anti-coagulant activity in *Nectandra* sp. is due to papain content (Carod-Artal and Vazquez Cabrera, 2007). The tree is considered psychodelic and toxic because it contains NMT (*N*-methyl tryptamine) and β-carboline. Dos Santos Filho and Gilbert (1975) detected the presence of indolalquilamine, *N*-methyl tryptamine and 6-methoxy-*Nb*-methyl-1,2,3,4-tetrahydro-β-carboline.

Starting with crude ethanol extracts of leaves, Da Silva Filho *et al*. (2004b), isolated three tetrahydrofuran lignans: nectandrin C, D, and E; and eight described previously: machilin G, galgravin, nectandrin A, nectandrin B, calopiptin, veraguensin, aristolignin and ganschisandrin.

Melo *et al*. (2004), isolated spatulenol from leaves of *N. saligna* (only from leaves in spring), alismol (only in autumn), two phenylpropanoids: elemicin and asaron; two neolignans: veraguensin and calopiptin. Liriotulipiferin (the aporphine alkaloid) was isolated by standard methods starting with bark methanol extracts.

De Luca *et al*. (2004) isolated three tetrahydrofuran lignans with activity against *T. cruzi* from leaves of *N. megapotamica.*

Ilza and Naría (2000) found cyanogenic glycosides in leaves using picro sodium paper.

Regarding essential oils (yielding 0.11-0.18 per cent), Romoff *et al*. (2010), determined the chemical composition in plant samples collected in São Paulo at different times of the year and hours of the day by GC-FID and GC-MS. They identified 19 compounds which were predominantly sesquiterpenes such as δ-elemeno (8.2-22.6 per cent) and α-bisabolol (62.3-69.4 per cent). They also found that there was a relatively large accumulation of oxygenated compounds during the month of February (70 per cent) compared with samples collected in August (63.9-65.1 most likely due to corresponding to decreases in sesquiterpene hydrocarbon levels. The structure of the major component, α-bisabolol, was later confirmed by NMR after purification. The monoterpenes identified: α-pinene, β-pinene, camphene, β-mircene and limonene, varied (1-9.3 per cent) depending on the season.

Torres *et al*. (2011c) characterized essential oils from *N. megapotamica* and found sesquiterpene hydrocarbon levels to be: 68.7 per cent in autumn, 58.4 per cent in spring and 62.1 per cent in summer. The major components found were: bicyclogermacrene (26.9 per cent, 24.6 per cent and 27.9 per cent), and germacrene D (17.8 per cent; 16.9 per cent and 18.5 per cent). The minor components found were: β-caryophyllene, δ-cadinene and δ-elemene. The monoterpene hydrocarbons were those in greatest abundance (24.7 per cent, 31.6 per cent and 21 per cent with α-pinene in highest amounts (9.8 per cent, 12.9 per cent and 9 per cent) followed by β-pinene (8.4 per cent, 10.6 per cent and 6.8 per cent) and limonene. Results obtained differed from

those of Romoff *et al*. (2010), for the same class of natural products from the same plant species. These investigators in contrast found α-bisabolol to be the major component of the oxygenated sesquiterpene fraction, as noted above. These differences might be attributed to regional differences in the climate of São Paulo (Brazil) versus Corrientes (Argentina) or a consequence of genetic difference within this species selected for different ecosystems to result in different ecotypes or chemotypes.

Background

The essential oil has antimicrobial anti-inflammatory and antitumor properties (Apel *et al.*, 2006), and alcohol extracts have analgesic and anti-inflammatory activities (Da Silva Filho *et al.*, 2004a). The root extracts have been used to alleviate muscle pain because of the analgesic and anti-inflammatory activities (Melo *et al.*, 2004).

Properties Tested

The analgesic and anti-inflammatory properties have been studied by Da Silva Filho *et al*. (2004a) using either crude alcohol extracts or isolated components (α-asarone, galgravin and veraguensin) at different doses. Bioassays used included testing abdominal contraction induced by acetic acid in mice, edema of paw induced by carrageenan in rats and the hot plate test with rats. All compounds showed activity in the abdominal contraction assay, but only α-asarone had activity in the hot plate test. Galgravin and veranguesin were active in the anti-inflammatory assay.

The same authors found that oral administration of 500 mg/kg of crude hydroalcoholic extract resulted in 82.2 per cent inhibition of contractions induced by acetic acid, and that 20 mg/kg dose of α-asarone, galgravin or veraguensin inhibited induced contractions 60.5 per cent, 71.3 per cent and 70.6 per cent respectively (2007a). Inhibition of carrageenan-induced paw edema was 41.2 per cent with veraguensin and 71.4 per cent with galgravin added at a dose of 20 mg/kg. Hot plate test activity was evident using either 20 mg/kg α-asarone or 300 mg/kg crude extract. In the *in vitro* assay COX-2 and NF-êB were inactive. The results suggest that veraguensin and galgravin have peripheral analgesic activity, while α-asarone is responsible for analgesic activities in the crude extract.

Apel *et al*. (2006) verified *in vitro* antimicrobial activity in essential oil which was able to inhibit growth of *S. aureus* 71 per cent and growth of *P. aeruginosa* 51 per cent. The material had no effect on growth of *E. coli* or *C. albicans*. Anti-inflammatory activity in oil was measured as inhibition of leukocyte migration (16.2 ± 3.8 mm in Borden boxes). The oil also has selective toxicity for prostate and multiple melanoma cancer cells. These results suggest that the essential oils can be used as a source of antimicrobial, anti-inflammatory and antitumor agents.

Trypanocidal activity in ethanol extracts and isolated components was investigated by Da Silva Filho *et al*. (2004b) using the trypomastigote form of the parasite. Crude extract used at 4 mg/mL was inactive perhaps due to antagonists or low lignan content, however, chlorofom extraction could be used to concentrate inhibitory activity such that this fraction at 2 mg/mL was 100 per cent active, with respect to purified components with highest activity, machilin G (IC_{50} 2.2 mM) and calopiptin (IC_{50} 4.4 mM).

Da Silva Filho *et al*. (2007b) studied the *in vitro* antileishmanial and antimalarial activities of seven tetrahydrofuran lignans isolated from *N. megapotamica*: machilin G and veraguensin had high activity, whereas galgravin, nectandrin A, nectandrin B, calopeptin and ganshisandrin were inactive against *L. donovani*. In assays against *Plasmodium falciparum*, it was found that calopeptin had moderate activity, but that machilin G, nectandrin B, veraguensin and ganshisandrin were inactive. Bioassays done with leaf ethanol extracts using *Artemia salina* or on microbial growth inhibition (*E. coli, S. aureus y P. aeruginosa*) indicated low toxicity.

With regard to *B. diporus* anti-venom activity, Torres (2011) found that essential oil of *N. megapotamica* had very low activity, in which large relative amounts of this were needed in the bioassays to obtain inhibition of *B. diporus* venom. Leaf essential oils from aqueous distillates obtained from material collected in autumn and spring were active in inhibiting venom coagulant activity, and leaf essential oils collected in autumn inhibited venom hemolysis and both preparations were active at a ratio of >1: 300 against venom-mediated proteolysis of casein.

Hexane extracts also had activity against venom-indiced serum clotting, but this activity was only present in spring and was only detected at very high extract: venom ratios (Torres *et al.,* 2008). Aqueous extracts obtained from plants in autumn and summer inhibited hemolytic activity (Torres *et al.,* 2007), whereas alcohol and hexane extracts showed proteolysis inhibitory activity in plant material collected year round (Torres *et al.,* 2010). A general conclusion is that *N. megapotamica* has very little anti-venom activity. This is reflected in the observations that anti-venom activities are not concentrated in a particular extract and that each specific activity also varies greatly with the stage of vegetative growth (Ricciardi *et al.,* 2008). While most people will tend to confuse the laurel amarillo (*N. angustifolia*) with the laurel negro (*N. megapotamica*), both species have anti-venom activity but clearly distinct activities. It is thus important to develop ways to easily distinguish these two species for use as well as collection and study (Torres, 2011).

Genus *Paederia*

Paederia brasiliensis (Hook. f.) Puff. (Rubiaceae), syn.: *P. diffusa* (Brittson) Standl.

Common Names

Bejuco blanco (Beni, Bolivia), bejuco hedion-do (Santa Cruz, Bolivia), boa, (Chacobo), yuraq waji, (quechua, Chapare), isopore (chiriguano), Janq'o waji (aymara, Yungas).

Background

Leaves can be folded in the form of a compress for treatment of snakebite (De Lucca and Zalles, 1992).

Genus *Peltodon*

Peltodon radicans Pohl. (Lamiaceae)

Common Names

Mbói-ka'á, yerba del colmillo de la víbora, solimán de la tierra, (Gonzalez Torres, 1997). Hortela do mato, parakarí (Toursarkissian, 1980).

Background

In Brazil properties promoting broncho-dilation have been attributed to this plant.

Chemical Constituents

In the active extract: aliphatic hydrocarbons, 3β-OH,β–amirin, 3β-OH,α-amirin, β-sitosterol, stigmasterol, ursolic acid**,** 2α,3β,19α-trihydroxy-urs-12-en-28-oic acid (tormentic acid), methyl 3β-hydroxy,28-methyl-ursolate, sitosterol-3-*O*-β-D-glucopyranoside, and stigmasterol-3-*O*-β-D-glucopyranoside (Rocha da Costa *et al.,* 2008).

Properties Tested

Neutralization of the main biological activities of venom from *C. durissus ruruima* and *B. atrox* (Cavalcanti-Neto *et al.,* 1996). The flower extracts had highest anti-edematogenic activity (Rocha da Costa *et al.,* 2008)

Genus *Persea*

Persea americana Mill. (Lauraceae), syn.: *Laurus persea* L., *Persea americana* var. *angustifolia* Miranda, *P. americana* var. *drymifolia* (Schltd. and Cham.) S.F. Blake, *P. americana* Schltd. and Cham., *P. edulis* Raf., *P. drymifolia* Cham.; *P. gratissima* Gaertn., *P. persea* (L.) Cokerell

Common Names

In Peru: palta (avocado) (Mejía and Rengipo, 1995)

Chemical Constituents

Persenone A and persenone B (Kim *et al.,* 2000), carotenoids: lutein, zeaxanthin, α-carotene, and β-carotene (Lu *et al.,* 2005); in seeds, phytohormones derived from abscisic acid: β-D-glucoside of the acid (1'*S*,6'*R*)-8'-hydroxyabscisic and β-D-glucoside (of this acid), (1'*R*,3'*R*,5'*R*,8'*S*)-*epi*-dihydrophaseic (del Refugio Ramos *et al.,* 2004).

The oil of the fruit is mainly monounsaturated fatty acids: oleic, linoleic, palmitic, palmitoleic, linolenic and stearic (in descending order of abundance) whose derivatives: (2*E*,5*E*,12*Z*,15*Z*)-1-hydroxyeicosa-2,5,12,15-tetraen-4-one, (2*E*,12*Z*,15*Z*)-1-hydroxy eicosa-2,12,15-trien-4-one, acetate of (5*E*,12*Z*)-2-hydroxy-4-oxoeicosa-5,12-dien-1-yl, and acetate of (2*R*)-(12*Z*,15*Z*)-2-hydroxy-4-oxoeicosa-12,15-dien-1-yl (Kawagishi *et al.,* 2001), in leaves there is a toxin, persin: (*Z*,*Z*)-1-(acetyloxy)-2-hydroxy-12,15-eicosadien-4-one (Oelrichs *et al.,* 1995).

Properties Tested

Aqueous extracts of leaves were shown to have analgesic and anti-inflammatory activities in laboratory animals (Adeyemi *et al.,* 2002).

- ✯ The persenones were shown to strongly inhibit generation of superoxide and nitric oxide (NO) in cell culture systems, acting as antioxidants preferentially suppressing the generation of free radicals,and having anti-inflammatory effects (Kim *et al.,* 2000).

- ✫ Ester and ketone derivatives of fatty acids were very effective in counteracting liver damage (Kawagishi *et al.*, 2001)
- ✫ Aqueous, ethanol and ethyl acetate extracts injected into mice simultaneously with *B. asper* venom completely inhibited the hemorrhagic activity of the venom. This activity was attributed to the action of catechins, flavones, anthocyanins and condensed tannins that can chelate zinc required for venom metalloprotease activity (Castro *et al.*, 1999), (Borges *et al.*, 2001).
- ✫ Persin was shown to have necrotic activity using mammary gland and myocaridial epithelia. Feeding leaves of *P. americana* to livestock causes an intoxication effect (Oelrichs *et al.*, 1995).

Genus *Petiveria*

Petiveria alliacea L. (Phytolaccaceae), syn.: *P. alliacea* L. var *alliacea*; *P. alliacea* var. *tetranda* (B.A. Gómez) Haumann

Common Names

Pipí, calauchín apacin, guiné, tipi is widely distributed in tropical Latin America.

Chemical Constituents

Essential oil is found throughout the plant, but is in greater abundance in root: benzyl-2-hydroxyethyl-trisulphide (Szczepanski *et al.*, 1972), trithiolaniacine (*cis* 3,5-diphenyl-1,2,4,-tritiolan), benzaldehye, benzoic acid and *trans*-stilbene (Adegosan, 1974), dibenzyl trisulphide and *trans*-N-methyl-4-methoxy proline (Sousa *et al.*, 1990), isoarborinol, isoarborinol cinnamate; in roots: dipropyl disulfide, dibenzyl sulfide, dibenzyl disulfide, dibenzyl trisulfide, dibenzyl tetrasulfide, benzylhydroxymethyl sulphide and di(benzyltritio) methane (Coelho Benevides *et al.*, 2001), benzaldehyde, benzyl alcohol, benzyl benzoate, *cis* and *trans*-stilbene, diethyl sulphide, dibenzyl trisulfide (Ayedoun *et al.*, 1998), *S*-benzyl-*L*-cysteine sulfoxide (Kubec and Musah, 2001), (*R*)-*S*-(2-hydroxyethyl) cisteine sulfoxide, along with (R_SR_C)- and (S_SR_C)-*S*-(2-hydroxyethyl)cisteine, also along with vestiges of derivative of *S*-methyl-, *S*-ethyl- and *S*-propylcisteine (Kubec *et al.*, 2002). Also, according to Kubec *et al*. (2003), the lachrymatory principle from roots is (*Z*)-thiobenzaldehyde *S*-oxide.

Genus *Pfaffia*

Pfaffia tuberosa (Spreng.) Hickey (Amaranthaceae), syn.: *Gomphrena tuberosa* Spreng.

Common Names

Batatilla de don Antonio, caáparí mirí (Ricciardi *et al.*, 1996), in Paraguay caá pari.

Genus *Philibertia*

Philibertia gilliesii Hook. and Arn. (Campanulaceae), syn: *Philibertia gilliesii* Hook. and Arn. var. *gracilis* (Don) T. Mey., *Sarcostemma gilliesii* (Hook. and Arn.) Decne

Common Names

Aru-cumaé (chiriguano),

Background

The decoction of leaves serves as an antidote against snakebite (De Lucca *et al.*, 1992).

Chemical Constituents

Extracts have cysteine type proteases with specific proteolytic activity; the extracts are also anti-inflammatory (Sequeiros *et al.*, 2003).

Genus *Pilocarpus*

Pilocarpus pennatifolius Lem. (Rutaceae), syn.: *P. pennatifolius* Lem. var. *selloanus* (Engl.) Hassl.(Domínguez, 1928); *P. selloanus* Engl.

Common Names

Aguarandio mirí, jaborandí (tupí) (Ricciardi *et al.*, 1996), jaborandí, jaborandí del Paraguay (Amorín, 1988), ybirá-taí, yaguarandí, jaborandí (Domínguez, 1928), in Paraguay yvyrá-taí.

Chemical Constituents

Alkaloids are in an approximate proportion of 1 per cent (Sawaya *et al.*, 2011), are derived from histidine (imidazole), pilocarpine, about 50 per cent of the total number of alkaloides, isopilocarpine, pilocarpidine, isopilocarpidine, pilosine, isopilosine, jaborine, jaborandine, jaboridine, carpiline (pilossine) as well as joboric and pilocarpic acids; terpenoids: α-pinene, limonene, myrcene; other constituents: 2-undecanone, sandaracopimaradiene, vinyl dodecanoate (Gaillard and Pepin, 1999).

Genus *Rumex*

Rumex brasiliensis Link (Polygonaceae), syn.: *R. obtusifolius* L., *R. cuneifolius* Campdera

Common Names

Lengua de vaca (Toursarkissian, 1980)

Rumex cuneifolius Campd. (Polygonaceae)

Common Names

Lengua de vaca, maquichi (Marzocca, 1997).

Rumex crispus L. (Polygonaceae)

Common Names

Lengua de vaca (Gonzalez Torres, 1997), romaza (Domínguez, 1928), (Gupta, 1995), (Cabrera and Zardini, 1978)

Background

Leaves macerated in cane brandy or spirits are applied directly to snake bites (González Torres, 1997).

Chemical Constituents

From roots: 1,5-dihydroxyanthraquinones and anthrone (Gunaydin *et al.*, 2002), chrysophanol (chrysophanic acid), parietin (3-methyl ether of emodin), and nepodin (musizin, 1,8-dihydroxy-2-acetyl-3-methylnaphthalene) (Gyung Ja *et al.*, 2004); species of *Rumex* have between 6.6 and 11.1 per cent oxalic acid (plant dry weight) and ingestion can result in toxicity typical of oxalate-induced toxicosis (Panciera *et al.*, 1990).

Also identified: aesculetin, α-ionone, α-terpineol, benzylbenzoate, benzylsalicylate, β-bisabolene, β-cyclocitralbrunfelsene, β-damascenone, β-eudesmol, β-safranal, brunfelsene, brunfelsamidine, elemol, 2-ethylfuran, farnesol, farnesyl, geraniol, geranyl hopeanine, ionones, isobutylsalicylate, lavandulal, limonene, linalool, linoleic acid, linolenic acid, manaceine, manacine, mandragorine, methylfurans, methylanisoles, myrcene, myristic acid, *n*-decane, *n*-heneicosane, *n*-heptadecane, *n*-heptane, *n*-hexadecane, nerolidol, *n*-nonadecane, nonanes, *n*-octane, *n*-pentacosane, *n*-pentadecane, neophytadiene, *n*-tricosane, ocimene, pentadecanoic acid, palmitic acid, pinoresinols, salicylic acid esters, scopoletin, scopolin, and terpinolene (Gunaydin *et al.*, 2002).

Rumex obtusifolius L. (Polygonaceae), syn.: *Acetosa oblongifolia* (L.) A. and D. Löve, *Rumex obtusifolius* ssp. *agrestis* (Fries) Danser, *R. obtusifolius* ssp. *sylvestris* (Wallr.) Rech. f., *R. obtusifolius* var. *sylvestris* (Wallr.) Koch

Common Names

Lengua de vaca (Marzocca, 1997).

Chemical Constituents

α-picolin (Wilkinson, 1958), anthraquinones: aloe-emodin, chrysophanol and emodin (Fairbairn and Muhtadi, 1972); there is a significant proportionproportion of flavonols: quercetin, kaempferol, miricetin, small amounts of isorhammnethin, as well as trace amounts of flavones: apigenin and luteolin (Trichopoulou *et al.*, 2000).

polyphenols and flavonoids confer antioxidant properties (Trichopoulou *et al.*, 2000).

Properties Tested

The latex or milk secreted from this plant has a high concentration of tannins and oxalic acid. A tincture of this plant can thus be useful for menopausal problems. The whole plant contains abundant iron (and is antianemic), phosphorus, tannins and glycosides (Ibáñez-Calero *et al.*, 2009). Compounds present may help cleansing of the digestive system and well as kidney (diuretic activities). Root components are considered safe for use as a laxative, and use is indicated in cases of constipation. Use is also indicated for treatment for eczema, a sluggish digestive system and in iron deficiency anemia. Applied externally, crushed leaves and roots have a healing effect on ulcers and skin sores (Cornara *et al.*, 2009).

Genus *Sapindus*

Sapindus saponaria L. (Sapindaceae), syn.: *S. divaricatus* Cambess.; *S. inaequalis* DC.

Chemical Constituents

In leaves, stems, fruits and seeds: saponins (3-β-*O*-[α-*L*-rhammnopyranosyl (1→3) β -*D*-glucopyranosyl] hederagenin) (Lemos *et al.*, 1992), carbohydrates and steroids; in stems and leaves: flavonoids; in new stems from stumps: tannins, essential oils and anthraquinones in seeds: β-sitosterol, α-amyrin and β-amyrin, and seeds and leaves: rutin, luteolin and 4-methoxyflavone (Wahab and Selim, 1985).

Properties Tested

Complete inhibition of the hemorrhagic effect of *B. asper* (Costa Rica) was found in rat bioassys after intradermal injection of aqueous, ethanolic or ethyl acetate extracts of plant material (Castro *et al.*, 1999). Compounds identified in these extracts considered to be responsible for the inhibitory effects include catechins, flavones, anthocyanins and condensed tannins.

Genus *Sapium*

Sapium glandulosum (L.) Morong (Euphorbiaceae), syn.: *Sapium aucuparium* Jacq.

Common Names

Kurupika'ý (Gonzalez Torres, 1997).

Background

According to González Torres (1997) infusions of leaves for drinking, and according to Parodi, decoction of wood and applicaiton of the sticky juice to wounds can be used to avoid potentially devastating results after being bitten by a coral snake or a rattlesnake.

Sapium haematospermum Müll. Arg. (Euphorbiaceae)

Common Names

Kurupika'ý, lecherón, pega pega, (Gonzalez Torres, 1997), blanquillo, curupí, curupicaí, (Toursarkissian, 1980), árbol de leche, blanquillo, cambí, curupí, curupí-caí, lecherón, pega-pega, lecherón, curupí-cay, curupí, pega-pega, (Domínguez, 1928), (Parodi and Dimitri, 1988).

Background

Parodi: prepare a decoction of the wood and apply the viscous juice on coral and rattlesnake bites to avoid fatal results.

Properties Tested

Alcohol extracts of stems and leaves of plants from Corrientes (Argentina) demonstrated *in vitro* activity inhibitory against blood coagulation caused by *B. diporus* venom (Torres *et al.*, 2008).

Sapium longifolium Huber (Euphorbiaceae), syn.: *S. longifolium* Müll. Arg. (Domínguez, 1928), (Parodi and Dimitri, 1988), *S. biglsadulosum* var. *lomgifolium* Müll. Arg.

Common Names

Kurupika'ý, (Gonzalez Torres, 1997), kurupytá, kurupi, kurupika'y, curupica, lecherón, pega-pega

Background

In Paraguay: effective against snakebite (Gonzalez Torres, 1997).

Genus *Sida*

Sida rhombifolia L. (Malvaceae).

Common Names

Arrowleaf Sida; typychá (Gonzalez Torres, 1997), afata, escobadura, mata alfalfa, pichana (Toursarkissian, 1980; Gupta, 1995).

Background

The leaves in a compress are effective against snakebite (Marzocca, 1997).

Chemical Constituents

The leaves contain relatively higher amounts of nutrients including protein, carbohydrates, fiber, fat as well as ash. The root containes ephedrine and saponin, choline, pseudoephedrine, β-phenethylamine, vascin, hipaphorine and related indole alkaloids (Ahmad *et al.,* 1976)

Sida spinosa L. (Malvaceae); *Sida spinosa* L. var. *spinosa*, syn.: *S. angustifolia* Lam.; *S. spinosa* L. var. *angustifolia* (Lam.) Griseb., *S.angustifolia* Lam. (Gonzalez Torres, 1997), *S. spinosa* L. var. *riedelii* (K. Schum.) Rodrigo, syn. *S. riedelii* K. Schum., *S. spinosa* L. var. *angustifolia* Lam. (Griseb.) f. *riedelii*. (K. Schum.)

Common Names

Típica, afata hembra

Chemical Constituents

Esters: 1-glyceryl eicosanoate; *p*-hydroxyphenylethyl *trans*-ferulate, ecdysteroids: 20-hydroxyecdysone, turkesterone; 20-hydroxyecdysone 20,22-monoacetonide, 20-hydroxy-24-hydroxymethyl ecdysone. (Darwish and Reinecke, 2003), also has unidentified alkaloids.

Genus *Sidastrum*

Sidastrum paniculatum (L.) Fryxel (Malvaceae), syn.: *Sida paniculada* L. (Ricciardi *et al.,* 1996).

Common Names

Malva-hú, makaguá-ka'á (Gonzalez Torres, 1997), cited by Martín Dobrizhoffer as macuanga caá (hierba del pato, duck grass)

Background

P. de Montenegro (1711) *comidas sus ojas verdes como una cuarta de ellas luego que pica la víbora y así mismo mascada y aplicada a la mordedura, queda sin lesión y sin accidentes el herido. Si hubiere algunas horas que haiga mordido se toma una dragma de sus polvos, ó ojas machacadas en vino tibio y asimismo se aplica a la herida* (sic)

(Green leaves taken as food after the snakebite is recommended. Also, they should be chewed and applied directly to the bite. Powdered material suspended in warm wine and applied to the bite wound is also useful)

Genus *Sinapis*

Sinapis alba L. (Brassicaceae), *syn.: B. alba* Rabenh. non L., *B. hirta* Moench; (Manfred, 1977), *B. alba* (L.) Boiss. (Parodi and Dimitri, 1988).

Common Names

Mostaza blanca (Parodi and Dimitri, 1988) (Manfred, 1977).

Chemical Constituents

Un roots and seeds: sinalbin and gluconasturtiin, and two aromatic glucosinolates (Kjaer, 1960).

Genus *Tabernaemontana*

Tabernaemontana catharinensis A. DC. (Apocynaceae) syn.: *T. australis* Müll. Arg., *Peschiera australis* (Müll. Arg.) Myers, *P. catharinensis* A. DC. Myers.

Common Names

Sapiranguí, jasmim, casca da cobra

Chemical Constituents

Indole alkaloids: 12-methoxy-4-methylvoachalotine (Batina *et al.*, 2000), coronaridine, voacangine, hydroxyindolenine voacangin; voacristin, hydroxylindolenin voacristin and 3-hydroxylcoronaridin (Pereira *et al.*, 2004).

Properties Tested

The alkaloids have antibacterial activity (Guida *et al.*, 2003); extracts of root bark have been shown to have inhibitory activity against the myotoxic and lethal venom of rattlesnake, *C. durissus terrificus*, and this activity was correlated with the presence of quaternary alkaloid 12-methoxy-4-methylvoachalotin (Batina *et al.*, 2000). Aqueous plant extracts were fractionated on Sephadex G-10, and active fractions neutralized indole alkaloids 12-methoxy-4-methylvoachalotine (Batina *et al.*, 2000), coronaridine, voacangine, hydroxyindolenine voacangin; voacristin, hydroxylindolenin voacristin and 3-hydroxylcoronaridin (Pereira *et al.*, 2004). Activity of the venom after intramuscular injection neutralized $2LD_{50}$ doses of crotoxin (de Almeida *et al.*, 2004). Aqueous extracts also partially neutralized the myotoxic acitivity of the two *B. jararacussu* myotoxins bothropstoxin-I (BthTX-I) (catalytically inactivated) and BthTX-II on preparations of rat soleus muscle as well as live animals. Reduction of the tissue

necrosis was observed without inhibition of PLA_2 activity for both myotoxins (Trombone *et al.,* 1999; Veronese *et al.,* 2005).

Genus *Teucrium*

Teucrium vesicarium Mill. (Lamiaceae), syn.: *T. inflatum* Sw.

Common Names

Makaguá-ka'á.

Chemical Constituents

Aerial parts of species in this genus are rich in furoclerodane diterpenes (Piozzi *et al.,* 1998)

Genus *Trixis*

Trixis divaricata (Kunth) Spreng. (Asteraceae), *Trixis divaricata* (Kunth). Spreng. subsp. *divaricata* (Ferrucci *et al.,* 2002).

Common Names

Juan de la calle, malva del monte, contraveneno (Rodríguez, 1980).

Properties Tested

Hexane extract of the aerial parts and essential oils and essential oil from aqueous distillates of plant material from Argentina inhibits procoagulant activity of *B. diporus* venom *in vitro* (Ricciardi *et al.,* 2008; Dellacassa *et al.,* 2008).

Genus *Uncaria*

Uncaria guianensis (Aubl.) Gmel. (Rubiaceae),

Common Names

In Peru: uña de gato (Mejía and Rengipo, 1995)

Chemical Constituents

Contains 2.1 per cent alkaloids (bark and roots) and mainly oxindole acid glycosides (Sandoval *et al.,* 2002).

Properties Tested

Activity promoting immune function: antileukemic, antitumor, antimutagenic and anti-inflammatory activity (Sandoval *et al.,* 2002).

Conclusions

Disgarding what are called white bites or dry bites in which the snake's venom is not injected, it can be estimated that in 30 to 35 per cent of the cases there is the additional danger of microbial infection such as tetanus. It is evident that some constituents in various plant species interact with a range of different toxic materials that are associated with a snake bite. In effect it appears that plant secondary metabolites can provide a range of protective agents with effects on snakebite and the snake's venom being only one example. The basic underlying mechanisms for anti-

venom compounds are to alter or reverse toxicity. In the case of anti-venom activities in plants we describe, characteristic common features for detoxification involve inducing analgesic or anti-inflammatory activities or both as in *Brunfelsia uniflora*, *Cynara scolymus*, *Dorstenia brasiliensis*, *Mikania glomerata* and *Trianosperma tayuya*. Some snake venoms cause the release of bradykinin which in turn causes a sharp drop in blood pressure, pain and contraction of smooth muscle in various organs. As such, most plants commonly used as alexiteric as having anti-venom activity in various products in effect act to reverse or inhibited the release of bradykinin (Biondo *et al.*, 2003). One well-described example would be the use of alcohol extract of Apocinacea *Mandevilla vellutina* root on rat uterus.

Anti-venom agents also might act by modifing primary, secondary or tertiary structure of enzymes and proteins of venom that mediate toxicity. The mechanisms may involve immobilization or some form of modification to inhibit or prevent activity. Many of the physiological responses originate by a stimulatory process involving a transmitter (endogenous or exogenous) that bind to a specific receptor in a "lock and key" manner to triggers some activity. A venom toxin may modify or provide an alternative key, *e.g.*, a toxin, or a product of toxic enzyme activity, to inactivate or disable normal cellular activity. Inhibition of ATPase, or as discussed phospholipase PLA_2 by ACA. Another possible mechanism in which specific plant compounds may counteract the effects of venom is by sequestration of metals needed as co-factors for enzymes mediating the toxic effects such as metalloproteinases.

Many mechanistic details remain to be explained as to why the mere ingestion or contact with the appropriate plant constituents may counteract the action of venom enzymes or toxins: cardiotoxins (cytotoxins), hemotoxins, hemolysins, hemorrhagins, myotoxins, necrotoxins, nephrotoxins, neurotoxins, proteases etc. The toxic effects of venom are varied and numerous in which nervous and muscle tissue can be severely affected, and with lethal consequences *in situ* if transported through the booldstream. There is no doubt that harnessing the diverse protective effects naturally provided by plants to counteract the lethality and discomfort of a snake bite would be a useful additional approach to treatment beyond that of heterologous antivenom serum.

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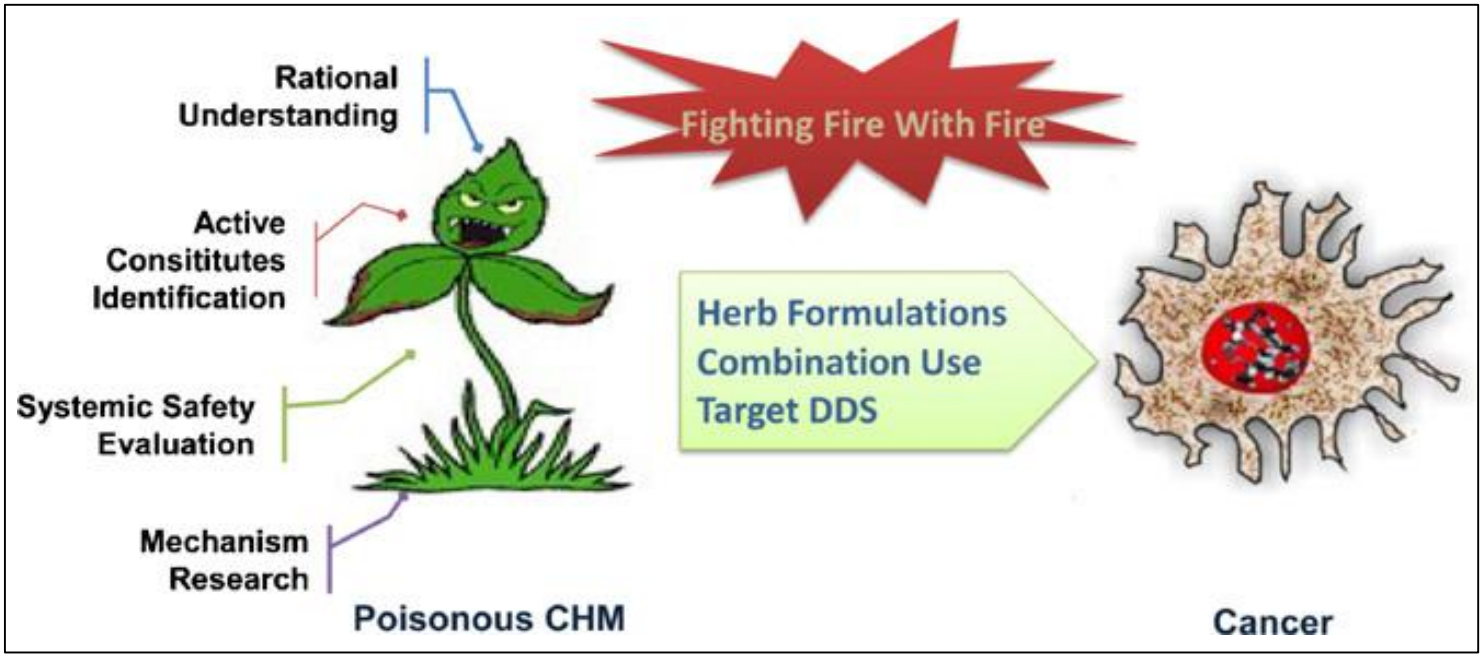

Figure 1.1: The research framework of PCHM is built up from many aspects, more sophisticated technologies and more suitable research methodologies are needed (Wang *et al.,* 2012).