Review article

Potential of the flora of Peru emphasizing in the Asteraceae family against *Trypanosoma cruzi*

Potencial de la flora del Perú enfatizando en la familia Asteraceae contra *Trypanosoma cruzi*

Guillermo E. Delgado-Paredes[1,2*] https://orcid.org/0000-0001-5769-8209
Paulo R. Delgado-Rojas[3] https://orcid.org/0000-0002-3518-1847
Consuelo Rojas-Idrogo[1,2] https://orcid.org/0000-0003-3525-6711

[1]Universidad Nacional Pedro Ruiz Gallo, Vicerrectorado de Investigación, Instituto de Biotecnología. Lambayeque, Perú.
[2]Universidad Nacional Pedro Ruiz Gallo, Facultad de Ciencias Biológicas, Ciudad Universitaria. Lambayeque, Perú.
[3]Universidad Particular San Martin de Porres, Facultad de Medicina Humana. Chiclayo, Perú.

[*]Corresponding autor: guidelg2015@yahoo.es

ABSTRACT

Introduction: American trypanosomiasis or Chagas diseases, caused by *Trypanosoma cruzi* and Human African trypanosomiasis, caused by *Trypanosoma brucei*, are two neglected tropical, endemic and fatal disease, that affect 20 million people and cause 95,000 deaths per year in tropical and subtropical areas of the world.

Objective: The objective of this review was to show the potential of the flora of Peru, emphasizing the Asteraceae family, against *Trypanosoma cruzi*, comparing it with American genera and species studied in various countries.

Methods: A review of scientific articles on the subject was carried out, especially taken from the Scopus, SciELO, ScienceDirect, Medline and PubMed databases of American plant species, covering a period of twelve years (2010 to 2022).

Results: A wide list of genera and species of the Asteraceae family and the flora of Peru with great potential in the treatment of trypanosomiasis is presented. Most of these species belong to the families Asteraceae, Piperaceae, Annonaceae, and Lauraceae. In the Asteraceae family, 48 genera and 76 species with trypanocidal activity were recorded, corresponding to 29 genera and 57 species for the flora of Peru. In these 29 genera, 174 endemic species potentially useful in the treatment of *T. cruzi* have been reported.

Conclusions: The flora of Peru has around 22,000 species. Some of these genera and species are found in the flora of various American countries and have been tested in the treatment of Chagas disease, so the flora of Peru offers new opportunities in its treatment.

Keywords: Chagas disease; crude extracts; medicinal plants; secondary metabolites; trypanosomiasis.

RESUMEN

Introducción: La tripanosomiasis americana o enfermedad de Chagas, causada por la *Trypanosoma cruzi* y la tripanosomiasis africana humana, causada por la *Trypanosoma brucei*, son dos enfermedades tropicales desatendidas, endémicas y fatales, que afectan a 20 millones de personas y causan 95 000 muertes por año en áreas tropicales y subtropicales del mundo.

Objetivos: El objetivo de esta revisión fue mostrar el potencial de la flora del Perú, enfatizar en la familia Asteraceae contra la *Trypanosoma cruzi* y compararlos con géneros y especies americanas estudiadas en diversos países.

Métodos: Se realizó una revisión de artículos científicos sobre el tema de especies vegetales americanas, especialmente tomados de la base de datos Scopus, SciELO, ScienceDirect, Medline and PubMed; se abarcó un período de 12 años (2010 a 2022).

Resultados: Se presenta una amplia relación de géneros y especies de la familia Asteraceae y de la flora del Perú con gran potencial en el tratamiento de la tripanosomiasis. La mayoría de estas especies pertenecen a las familias *Asteraceae*, *Piperaceae*, *Annonaceae* y *Lauraceae*. En la familia *Asteraceae* se registraron 48 géneros y 76 especies con actividad tripanocida; correspondieron

29 géneros y 57 especies para la flora del Perú. Asimismo, en estos 29 géneros se han reportado 174 especies endémicas potencialmente útiles en el tratamiento de la *T. cruzi*.

Conclusiones: La flora del Perú tiene alrededor de 22 000 especies. Algunos de estos géneros y especies se encuentran en la flora de varios países americanos y han sido ensayados en el tratamiento de la enfermedad de Chagas, por lo que la flora del Perú ofrece nuevas oportunidades en su tratamiento.

Palabras clave: enfermedad de Chagas; extractos crudos; plantas medicinales; metabolitos secundarios; tripanosomiasis.

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Introduction

Trypanosomiasis is a tropical disease caused by *Trypanosoma* spp., a protozoan of the Trypanosomatid family. The human diseases caused by trypanosomatids are leishmaniasis (*Leishmania* spp.), Human African trypanosomiasis or sleeping sickness (*Trypanosoma brucei*) and American trypanosomiasis or Chagas disease (*Trypanosoma cruzi*). These diseases are originally transmitted by contact with infected blood-sucking insects (reduviid insects), blood transfusion, vertical transfer from mother to fetus, organ and tissue transplantation, oral ingestion in sylvatic/rural environments, contact with infected conjunctiva or oral mucosa, sharing of contaminated syringes and laboratory accidents.[1,2] Trypanosomiasis is part of a group of 17 parasitic infections that also includes dengue, rabies, trachoma, human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy, Buruli ulcer, echinococcosis, lymphatic filariasis, onchocerciasis, schistosomiasis, dracunculiasis (Guinea worm disease), foodborne trematodiases, taeniasis/cysticercosis, soil-transmitted helminth infection, and yaws.[3] Fortunately, there are many efforts by various actors in the control and treatment of these diseases known as neglected tropical diseases (NTDs).[4,5].

Chagas disease is considered as a major public health problem in Latin America, estimating the approximately 10 millon people are infected and 100 millon are at risk worlwide, mainly due to migration of the population.[6] Likewise, it was also reported that between six and seven million people are affected by this infection;[7] however, recently trypanosomatids have been reported to affect about 20 million people in the world's poorest countries, leading to 95,000 deaths per year, and their incidence is often associated with “malnutrition, weak immune system, low quality housing, and population migration”.[8]

In Peru, the pioneer researcher on Chagas disease was the doctor Edmundo Escomel (1880-1959), who reported the presence of *Triatoma infestans* in Arequipa and thus described the first human case of the disease in Peru.[9] However, studies carried out in Peru on the trypanocidal activity of native plants are few. In a study carried out by Peruvian researchers using the essential oils of ten plant species, mostly introduced, only EO of *Cymbopogon citratus* (DC.) Stapf (Poaceae) and *Aloysia triphylla* Paláu (Verbenaceae) inhibited the growth of *T. cruzi* epimastigote form.[10] In another study carried out by Spanish scientists on eight species from the Peruvian Amazon, only *Cedrela odorata* L. (Myrtaceae) and *Aristolochia pilosa* Kunth (Aristolochiaceae) were the most active against *T. cruzi*, followed by *Tabebuia serratifolia* (*Handroanthus serratifolius* (Vahl) S.O. Grose (Bignoniaceae), *Tradescantia zebrina* Heynh. ex Bosse (Commelinaceae) and *Zamia ulei* Dammer (Zamiaceae).[11] Added to these is the study on the trypanocidal activity of *Piper solmsianum* C. DC. (Piperaceae) on epimastigote and trypomastigote forms of *T. cruzi*.[12]

The objective of this review was to show the potential of the Peruvian flora, emphasizing the Asteraceae family, against *Trypanosoma cruzi*, comparing it with American genera and species studied in various countries, based on ethnobotanical utility and complemented by phytochemical and pharmacological studies.

Methods

The methodology included a literature review of articles regarding the use of crude extracts and pure substances, obtained from American flowering plant species, in the treatment of Trypanosoma cruzi. No language restriction was made, although the vast majority of the articles consulted were in English and very rarely in Spanish. This literature review covered most of the studies conducted in the last twelve years (2010 to 2022). Exceptionally, studies carried out in years prior to 2010 were included, when they were carried out on highly promising plant species and on the treatment of *Trypanosoma brucei*, when *T. cruzi* was also included. In most cases Scopus database was use as well as SciELO, Science Direct, Medline and PubMed. The following keywords were used in the search, mainly word combinations: *Trypanosoma cruzi*, Chagas Disease, secondary metabolites, plant species, chemical composition. These keywords were the filter used in the search and selection of the articles.

The order of presentation of the plant families is based on the evolutionary position proposed by APG IV[13] and Christenhusz and Byng,[14] from the most primitive to the most evolved, with the exception of the families indicated in the regional flora and miscellaneous families. The comparisons with the species of the flora of Peru were made based on two important studies: Catalogue of the Flowering Plants and Gymnosperms of Peru[15] and "Diez años de Adiciones a la Flora del Perú: 1993-2003".[16]

Results

Current chemotherapy against Chagas disease

The chemotherapeutic treatment is the main therapy traditionally used to control of numerous parasitic infections like Chagas disease. However, the current treatment and drugs available are scarce, highly toxic, costy, lengthy, and often ineffective, with several secondary effects, requiring hospitalization some times.[17,18,19,20]

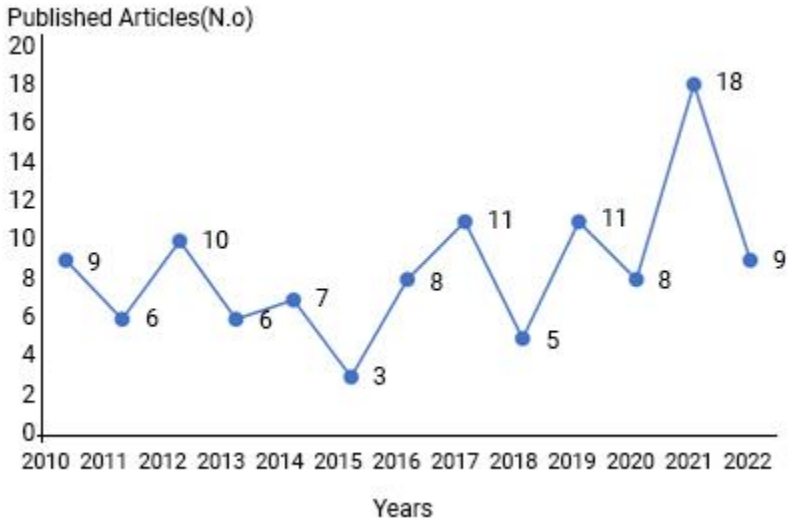
The two main drugs used for the treatment of Chagas disease since the end of 60' decade have been Lampit® (Nifurtimox) and Rochagan® (Benznidazole). In addition, Fungizone® (Amphoterecin B) is other drug that can be used as a second line treatment using nano-drug delivery systems. Recently, the trial of several drugs in the treatment against Chagas disease such as Biosynth® (Albaconazole); Milteforan® (Edelfosine); Rimidin® (Fenarimol); Sigma-Aldrich® (Ilmofosine); Nizoral® (Ketoconazole); Milteforan® (Miltefosine); Sigma-Aldrich® (Benznidazole nanoformulated), among others, has been reported; however, the results are under evaluation and are not definitive.[21,22] An extensive literature review on new drugs used in the treatment of Human African Trypanosomiasis has been recently published by Dickie *et al*[23] and De Koning.[24]

The current pharmacological treatment for Chagas disease is using nifurtimox and benznidazole, but unfortunately these drugs are relatively toxic for adult patients and require prolonged administration. On the other hand, many scientists in the world have oriented their research towards the search for plant species with potential utility in the treatment of several diseases,[25] as in this case trypanosomiasis. Two significant reviews in this regard have been reported by research groups in Rio de Janeiro[18] and Minas Gerais,[26] both located in Brazil, where the disease was discovered.

Families of American and Peruvian plant species used against *T. cruzi*

The results on families, genera and species of American plants with emphasis on species of the flora of Peru and families listed evolutionarily, are summarized in table 1. This list includes 34 families, 122 genera and 115 species, including American species in general, species reported for the flora of Peru and species of specific regional flora. In the Asteraceae family, 48 genera and 76 species with trypanocidal activity were recorded, corresponding to 29 genera and 57 species for the flora of Peru. In these 29 genera, 174 endemic species potentially useful in the treatment of *T. cruzi* have been reported, highlighting the genera *Pentacalia* (21), *Verbesina* (21), *Baccharis* (20), *Vernonia* (20) and *Mikania* (18).

In total, 112 articles published between 2010 and 2022 were reviewed. Figure 1 shows the number of scientific publications per year.



Source: Own elaboration.

Fig. 1 – Scientific articles, published between the years 2010 to 2022, on the activity of various secondary metabolites isolated from numerous plant species, against *Trypanosoma cruzi*.

The families considered in the study are the following:

1. **Winteraceae:** One on the most primitive family among basal angiosperms. Crude extracts from stem bark of *Drimys brasilienses* Miers, shrub or small tree collected in Umuarama, Campos do Jordão, São Paulo (SP)-Brazil, and its main derivative, the sesquiterpene polygodial, were tested against trypomastigotes of *T. cruzi*, but only polygodial showed high parasite selectivity with IC_{50} = 2.0 µg/mL.[27]
2. **Piperaceae:** Among the basal angiosperm highlights the Piperaceae family. Leaves extract of *Piper regnelli* (Miq.) C. DC. var. *pallescens* (C. DC.) Yunck., collected on the campus of the State University of Maringá in Paraná-Brazil, showing that the neolignan eupomatenoid-5 exhibited activity against trypomastigotes (IC_{50} = 40.5 µM).[28] Essential oil (EO) from leaves of *Piper aduncum* L., collected in Medicinal Plants Garden of the Universidade Federal de Lavras, Minas Gerais-Brazil, with its main constituent linalool and nerolidol, was effective against trypomastigotes (IC_{50} = 2.8 µg/mL) and metacyclic (IC_{50} = 12.1 µg/mL) trypomastigotes, as well as amastigotes (IC_{50}

= 9 µg/mL), during 24 h.[2] Likewise, stem extracts (IC_{50} = 50 µg/mL) from adult plants of *Piper solmsianum* C. DC., collected in the Núcleo de Picinguaba, Ubatuba, SP-Brazil, showed inhibitory activity against epimastigotes and 6-8 monts-old *in vitro* plants (IC_{50} = 50 µg/mL) and grandisin (IC_{50} = 25 µg/mL) against trypomastigotes.[12]

In leaves extract from *Piper malacophyllum* (C. Presl.) C. DC., collected in Parque Estadual Intervales (Sisbio 15780-2), SP-Brazil, were isolated one alkenylphenol, gibbilimbol B, showing activity against trypomastigotes with IC_{50} = 17 µg/mL.[29] Others lignans such as the dibenzylbutyrolactone (-)-cubebin and (-)-hinokinin showed a significant parasitemia reduction in animals treated with oral administration of these compounds.[30] Likewise, a new furofuran lignan, (1S,3aS,4S,6aS)-1-(3',4'-dimethoxyphenyl)-4-3'',4''methylendioxyphenyl) hexahydrofuro[3,4-c] furan, isolated from leaves of *Piper jericoense* Trel. & Yunck., collected in Puerto Triunfo, Antioquia, Colombia, were active against epimastigotes, amastigotes and trypomastigotes.[31]

3. **Aristolochiaceae:** In leaves extract from *Aristolochia cymbifera* Mart. & Zucc., collected from The Instituto Plantarum de Estudos da Flora, SP-Brazil, the dibenzylbutyrolactone lignan Kusunokinin with significant activity against amastigotes (IC_{50} = 17 µM) and trypomastigotes (IC_{50} = 51 µM), and copalic acid (ENT labdane diterpene) (IC_{50} = 39.5 µM), were the most active compounds.[32]
4. **Annonaceae:** In the volatile oil extracted from leaves of *Annona crassiflora* Mart., collected in Horto Florestal Andrade Silva in Avaré, SP-Brazil, with the major constituents α-amorphene (43.6%) and E-caryophyllene (17.7%), showed the highest activity against trypomastigotes (IC_{50} = 5.31 µg/mL), nine folds higher than benznidazoles and more active than those of the other *Annona* species.[33] In the EO of the leaves from *Annona coriacea* Mart., collected in the Estação Ecológica of the Instituto Florestal of SP, at Águas de Santa Bárbara, Brazil, bicyclogermacrene was its major compound (39.8%), showing activity against trypomastigotes.[34]

5. **Lauraceae:** Neolignans licarin A isolated from the green fruits of *Nectandra glabrescens* Benth., and burchellin isolated from *Ocotea cymbarum* Kunth, collected in northeastern Brazil (Belém-Pará), were tested against epimastigotes, showing growth inhibition in 45% with licarin A and 20% with burchellin with an IC_{50}/96 h of 462.7 and 756 µM, respectively.[35]

   In leaves of *Nectandra oppositifolia* Nees & Mart., collected in Artur Nogueira city, SP-Brazil, licarin A was isolated and displayed activity against trypomastigotes, where the derivative of licarin A, 2-allyl, showed the highest activity against trypomastigotes (IC_{50} = 5.0 µM) and the heterocyclic derivative displayed IC_{50} = 0.5 µM. Others different simplified structures of licarin A as vanillin and its acetyl derivative displayed activity against amastigotes (IC_{50} = 5.5 and 5.6 µM, respectively).[36] In another study conducted on leaves extract from *N. oppositifolia*, collected at Artur Nogueira city, SP-Brazil, the flavonoids kaempferol, and kaempferol-3-O-α-(3,4-di-E-p-coumaroyl)-rhamnopyranoside were effective against trypomastigotes with IC_{50} = 32.0 and 6.7 µM, respectively.[37] In leaves and twigs extracts from *N. oppositifolia*, ethyl protocatechuate (IC_{50} = 18.1 µM), and its respective n-propyl, n-butyl, n-pentyl, and n-hexyl esters exhibited IC_{50} values (20.4 to 11.7 µM) against amastigotes.[38] In n-hexane leaves extract from *Nectandra leucantha* Nees & Mart., a tree native to the tropical Atlantic Forest area of Cubatão city, SP-Brazil, four related neolignans showed trypanocidal activity (IC_{50} = 15.2-86.5 µM),[39] as well as its dehydrodieugenol derivatives.[40] In *Nectandra megapotamica* (Spreng.) Mez, leaves extract the compound machilin G was the most active against trypomastigotes (IC_{50} = 2.2 µM).[41]

   In *Aniba* Amazonian species, *Aniba panurensis* (Meisn.) Mez, *A. parviflora* (Meisn.) Mez and *A. rosaedora* Ducke were isolated and identified three styrylpyrones, a pyridine alkaloid and two kavalactones; however, only *A. panurensis* extracts showed *in vitro* activities against *T. cruzi*. [42]

6. **Calophyllaceae:** Mammea A/BA (93.6%) and the mixture of coumarins (mammea A/BA + A/BB + A/BD) (86:10:1%), isolated from *Calophyllum brasiliense* Cambess, collected in Tropical Rain Forest, Tathuicapan de

Juárez, Veracruz-Mexico, showed high trypanocidal activity than the current drug benznidazole of three Mexican strains of *T. cruzi*.[43] Likewise, Mammea A/BA showed LC_{50} = 85.8 and 36.9 µM for epimastigotes and trypomastigotes, respectively, inducing apoptotic cell death of *T. cruzi*.[44] Mammea A/AA was obtained from the fruit peels of *Mammea Americana*,[45] commonly known as "mamey", an edible fruit with a very pleasant taste and smell.

7. **Salicaceae:** In leaves extract from *Casearia sylvestris* Sw., collected from Atlantic Forest area in SP-Brazil, four active clerodane diterpenes (casearins A, B, G, and J) were isolated, observing activity against trypamastigotes (IC_{50} = 0.53 to 2.77 µg/mL).[46] The sesquiterpene (-)- T-Cadinol, isolated from leaves extract showed activity against trypomastigotes and amastigotes with IC_{50} = 18 and 15 µM, respectively.[47]
8. **Euphorbiaceae:** Aqueous extract obtained from the roots of *Croton heliotropiifolius* Kunth was evaluated for its *in vitro* antiparasitic activity against *T. cruzi* showing a weak antiparasitic effect.[48]
9. **Vochysiaceae:** Fractions from the leaves extract of *Qualea grandiflora* Mart., collected in the Brazilian Cerrado, were evaluated against *T. cruzi* observing that three fractions had a moderate activity (>100 µg/mL).[49]
10. **Myrtaceae:** Fruits extracts of *Eugenia uniflora* L., collected in the municipality of Crato, Ceará-Brazil, showed anti-*T. cruzi* activity against epimastigotes (IC_{50} = 62.76 mg/mL).[50]
11. **Sapindaceae:** Chromatographical fractions from dried fruit resin and also pure compounds of *Sapindus Saponaria*, collected in Medellin-Colombia, were evaluated against *T. cruzi*, observing that caused low viability on amastigotes (1A: 6.21% and 2A: 9.86%).[51]
12. **Rutaceae:** Leaves extracts of *Zanthoxyllum chiloperone* var. *angustifolium* Engl., collected in Pirebebuy, Cordillera, Paraguay, were evaluated against trypomastigotes and amastigotes, observing that canthin-6-one and 5-methoxy-canthin-6-one, showed activity against trypomastigotes and amastigotes (IC_{50} = 15.1 µM).[52]

13. **Malvaceae:** In stem barks of *Luehea ochrophylla* Mart., native to Central and South American, it was observed that HEX, DCM and EtOH extracts and fractions exhibited activity against amastigotes and trypomastigotes, with IC_{50} = 30.0, 25.6 and 28.1 µg/mL, respectively, and the isolated compounds were friedelin, β-friedelinol, lupeol, and others.[53]
14. **Solanaceae:** The antiprotozoal activity of the terpenes dehydroabietic acid, dehyroabietinol, oleanolic acid and 34 synthetic derivatives, isolated from the aerial parts of *Fabiana imbricata* Ruiz & Pav., native to dry mountain slopes in Chile and Argentina, were evaluated against epimastigotes noting that the activity of the compounds was moderate (IC_{50} = 43 to > 256 µg/mL).[54]
15. **Verbenaceae:** Aerial parts of five species of *Lippia*, *L. alba* (Mill.) N.E.Br. ex Britton & P. Wilson, *L. citriodora* (L'Hér.) Kuntze, *L. micromera* Schauer., *L. origanoides* Kunth and *L. dulcis* Trev., collected in different places of Colombia as Armenia, Boyacá, Bucaramanga, and others places, were tested against *T. cruzi*, observing that EO of *L. alba* exhibited the highest activity against epimastigotes (IC_{50} = 5.5 µg/mL) and amastigotes (12.2 µg/mL), while thymol (IC_{50} = 3.2 µg/mL) and S-carvone (IC_{50} = 6.1 µg/mL) were active on amastigotes.[55] EO with monoterpenes and sesquiterpenes of *L. sidoides* Cham. and *L. origanoides*, were the most potent trypanocidal activity against trypomastigotes and amastigotes, respectively.[56] Likewise, EO of *L. sidoides* and *L. origanoides*, collected from Medicinal and Aromatic Plants of the Federal University of Piaui, Teresina-Brazil, showed that, in epimastigotes and trypomastigotes, induced a significant reduction in the percentage of macrophages infected.[57]
16. **Lamiaceae:** Essential oils of *Rhaphiodon echinus* (Nees & Mart.) Schauer., no was active against the epimastigotes.[58]
17. **Asteraceae:** This family is rich in species used in the treatment of *T. cruzi*, having initially reported 222 genera with 14 endemics for the flora of Peru, as well as 1,432 species with 729 endemics.[15] To this was added later 230 new species in 29 new genera and others already reported.[16]

In aerial parts from *Achillea ptarmica* L., collected from the Institute of Pharmaceutical Biology and Phytochemistry, Münster-Germany, the isolated alkamides, pellitorine and 8,9-Z-dehydropellitorine, showed activity against amastigotes.[59] Twenty-seven species of Asteraceae, collected in several countries, showed activity, and between these species, deoxymikanolide isolated from *Mikania micrantha* Kunth, and (+)-15-hydroxy-labd-7-en-17-al isolated from *Aristiguietia glutinosa* (Lam.) R.M. King & H. Rob. showed *in vivo* activity against *T. cruzi*.[60]

In aerial parts of *Stevia satureiifolia* (Lam.) Sch. Bip. ex Klotzsch, collected in province of Entre Ríos-Argentina, the flavonoids eupatorine and 5-desmethylsinensetin showed activity against epimastigotes and trypomastigotes with IC_{50} = 0.2 and 0.4 µg/mL, and 61.8 and 75.1 µg/mL, respectively.[61] The sesquiterpene lactones eupatoriopicrin, estafietin, eupahakonenin B and minimolide, isolated from Argentinean Asteraceae species, *Stevia maimarensis* (Hieron.) Cabrera, *S. alpina* Griseb., *S. gilliesii* Hook. & Arn. and *Mikania minima* (Baker) B.L. Rob., respectively, were active against epimastigotes, resulting eupatoriopicrin the most active compound (IC_{50} = 2.3 µg/mL).[62] The action mode of the sesquiterpene lactones eupatoriopicrin and estafietin, isolated from *S. alpina* and *S. maimarensis*, respectively, it can be considered a promising alternative for the treatment of Chagas' disease.[63] In addition, four sesquiterpenes lactones derivatives synthesized from estafietin, isolated from *S. alpina*, showed activity against *T. cruzi*, and epoxyestafietin was the most active compound against trypomastigotes (IC_{50} = 18.7 µg/mL) and amastigotes (IC_{50}=2.0 µg/mL).[64] Grandiflorenic acid, one of the main kaurene diterpenes, isolated from different parts of *Sphagneticola trilobata* (L.) Pruski, affected the viability of *T. cruzi* with IC_{50} = 24.6 nM.[65]

The sesquiterpenes lactones, cynaropicrin and psilostachyin A, isolated from *Cynara scolymus* L. and *Ambrosia tenuifolia* Spreng., respectively, showed activity against trypomastigotes and amastigotes.[66] In *A. tenuifolia* was also studied the activity of psilostachyins (psilostachyins A and C) as trypanocidal compounds.[67] In *Tessaria absinthioides* (Hook. & Arn.) DC and *Flourensia oolepis* S.F. Blake derivatives compounds obtained from tessaric acid and ilicic acid were the most

active against *T. cruzi* with IC_{50} = 9.3 and 8.8 µM, respectively.[68] The extract from aerial parts of *Ageratum fastigiatum* (Gardner) R.M. King & H. Rob. showed activity against *T. cruzi*, while the phytochemical screening revealed the presence of coumarins (ayapin), terpenes/sterols, and flavonoids.[69] In *Parthenium hysterophorus* L., *Decachaeta incompta* (DC.) R.M. King & H. Rob. and *Vernonia liatroides* DC., the sesquiterpenes lactone ambrosin was most effective (IC_{50} = 67.1 µM) than incomptine B (IC_{50} = 123.7 µM) and glaucolide E (IC_{50} = 215.1 µM) and all of these were more potent than the drugs benznidazole and nifurtimox.[70]

Several species of the *Baccharis* genus have been evaluated for their trypanocidal potential. The flavonoids naringenin and sakuranetin isolated from the dried leaves of *B. retusa* DC., collected from Campos do Jordão, SP-Brazil, showed activity against trypomastigotes (IC_{50} = 20.17 µg/mL).[71] In previous studies this species showed potential activity against trypomastigotes (IC_{50} = 20.39 µg/mL).[72] In new studies conducted on extract from the aerial parts of *B. retusa*, also collected from Campos do Jordão, were isolated and characterized three actives related diterpenes: ent-15β-senecioyl-oxy-kaur-16-en-19-oic (1), ent-kaur-16-en-19-oic (2) and ent-16-oxo-17-nor-kauran-19-oic (3) acids, compounds that were effective against trypomastigotes with IC_{50}=3.8 (1), 75.3 (2) and 44.2 µM (3), respectively.[73] In extract of the aerial parts of *B. uncinella* DC., collected from Campos do Jordão, were identified the cinnamic acid derivatives [caffeic acid (1)] and two flavones [(hispidulin (3) and pectolinaringenin (4)] and a mixture of three chlorogenic acids (5), observing that compounds 4, 3 and 1 showed the highest activity against trypomastigotes (IC_{50} = 52, 81 and 56 µg/mL, respectively), while compound 5 showed IC_{50} = 61 µg/mL.[74] In oils of inflorescence of *B. spicata* (Lam.) Baill. and *B. punctulata* DC., β-Pinene, limone, and spathulenol oxide were detected in both species, but only (-)-alismol in *B. punctulata*, inhibits the growth of epimastigotes (IC_{50} between 2.15 and 12.49 µg/mL).[75] Likewise, in extract from aerial parts of *B. sphenophylla* Dusén ex Malme, three diterpenes were evaluated, observing that ent-kaurenoic and 15β -tiglinoyloxy-ent-kaurenoic acids showed activity against trypomastigotes.[76] In this same species, the extract from aerial parts displayed activity against amastigotes, where the compounds 7α-hydroxy-ent-abieta-

8(14),13(15)-dien-16,12β-olide and hexacosyl p-coumarate showed effectiveness with IC_{50} = 21.3 and 16.9 µM, respectively.[77]

Parthenoloide, isolated from leaves of *Tanacetum vulgare* L., collected in Irenice Silva Medicinal Plants Garden of the University of Maringá, Brazil, and evaluated for the synergistic effects with benznidazole against epimastigotes and trypomastigotes, showed a strong activity with IC_{50} = 1.6 to 0.07 µg/mL, reducing 23-fold the concentration of benznidazole.[78] In aerial parts of *T. parthenium* (L.) Sch.Bip., collected from Laboratório Botânico Flores & Ervas, Piracicaba, SP-Brazil, guaianolide was effective against epimastigotes (IC_{50} = 18.1 µM) and amastigotes (IC_{50} = 66.6 µM) of *T. cruzi*. [79] Alcoholic leaves extract of *Castanedia santamartensis* R.M. King & H. Rob. displayed activity against *T. cruzi*, with kaurenoic acid as the major component.[80] Extracts from *Helichrysum italicum* (Roth) G. Don and *Crithmum maritimum* L. (Apiaceae), were evaluated against amastigotes observing that the extract (falcarindiol, as one major compound) and the fraction 1 from flowers of *C. maritimum* were the most active (EC_{50} = 0.47 µg/mL).[81]

In extract leaves from *Calea uniflora* Less., collected from Imbituba, Santa Catarina-Brazil, ethyl caffeate and the mixture of butein and orobol demonstrated trypanocidal effect against amastigotes with IC_{50} = 18.27 and 26.53 µM, respectively.[82] Likewise, were also identified and evaluated four germacranolide-type sesquiterpene lactones; nevertheless, none of the isolated compounds showed trypanocidal effect.[83] In extract leaves of *C. pinnatifida* (R. Br.) Less., collected in "Costa da Lagoa", Florianópolis-Brazil, a new furanoheliangolide sesquiterpene lactone named 11,13-dihydroxy-calaxin showing activity against trypomastigotes (IC_{50} = 5.27 µM).[84] Dewaxed extract of *Urolepis hecatantha* (DC.) R.M. King & H. Rob. showed activity against epimastigotes (IC_{50} = 7 µg/mL) and the sesquiterpene lactones eucannabinolide and santhemoidin C were active on *T. cruzi*.[85]

Other Asteraceae species of the genera *Gochnatia*, *Vernonia*, *Pentacalia*, *Aldama* and *Mikania* have also shown trypanocidal potential. Extract, fractions, and compounds of *Gochnatia pulchra* Cabrera, an Asteraceae present from Mexico to Argentina, showed moderate activity against promastigotes of *L. amazonensis*,

specifically apigenin;[86] therefore, this species is potentially useful against *T. cruzi*. The natural product lupeol, ten lupeol derivatives 2-11 and five new esters derivatives 7-11, isolated from aerial parts (leaves and flowers) of *Vernonia scorpioides* (Lam.) Pers., showed activity against *T. cruzi*, especially the derivative 6 (IC_{50}=12.48 µg/mL).[87] EO from leaves, flowers and roots of *V. brasiliana* (L.) Druce, collected in Monte Alegre de Minas, Minas Gerais-Brazil, showed activity against *T. cruzi* with IC_{50}=72, 88 and 70 µg/mL, respectively.[88] Fourteen plant extracts and seventeen sesquiterpene lactones from the South American tribe Vernonieae (Asteraceae) were evaluated against *T. cruzi*, observing the best results with leaves and flowers rinse extracts from *Vernonanthura nebularum* Cabrera (H. Rob.) and *Elephantopus mollis* Kunth (IC_{50} values < 2 µg/mL).[89]

The bioactive compound, jacaranone, isolated from the leaves of *Pentacalia desiderabilis* (Vell.) Cuatrec., collected in Campos do Jordão, SP-Brazil, showed activity against trypomastigotes (IC_{50} = 13.0 µg/mL).[90] The ent-3-α-hydroxy-kaur-16-en-18-ol, three new diterpenes, namely, ent-7-oxo-pimara-8,15-diene-18-ol, ent-2S,4S-2-19-epoxy-pimara-8(3),15-diene-7β-ol and ent-7-oxo-pimara-8,15-diene-3β-ol, and sesquiterpene lactones budlein A, isolated from leaves extract of *Aldama discolor* (Baker) E.E. Schill. & Panero, endemic from the Brazilian "Cerrado" (Sacramento, Minas Gerais-Brazil), showed *in vitro* activity against amastigotes.[91] In *Artemisia copa* Phil. were observed and identified several phenolic acids and flavonoids with activity against *T. cruzi* (LD_{50} = 131.8 µg/mL).[92] In leaves extract from *Inula viscosa* [*Dittrichia viscosa* (L.) Greuther] the sesquiterpene lactones 8-*epi*-xanthatin-1β,5β-epoxide and inuloxin A (IC_{50} values between 4.99 and 14.26 µM) showed more activity against epimastigotes.[93]

The organic and aqueous extracts of aerial parts from four Argentinean *Mikania* species, *M. micrantha* Kunth, *M. parodii* Cabrera, *M. periplocifolia* Hook. & Arn. and *M. cordifolia* (L. f.) Willd., collected in Entre Ríos-Argentina, showed activity against epimastigotes at 10 µg/mL [94] In species of this same genus, three sesquiterpene lactones, mikanolide, deoxymikanolide and dihydromikanolide, isolated of *M. variifolia* Hieron and *M. micrantha*, collected in Entre Rios and Tucumán-Argentina, respectively, were active against epimastigotes (IC_{50} = 0.7, 0.08 and 2.5 µg/mL, respectively), trypomastigotes (IC_{50} = 2.1, 1.5 and 0.3 µg/mL, respectively) and

amastigotes (IC_{50} = 4.5, 6.3 and 8.5 μg/mL, respectively).[95] Likewise, in these species, collected in Entre Rios and Tucumán-Argentina, respectively, deoxymikanolide was evaluated for its *in vitro* activity on epimastigotes and *in vivo* activity on an infected mouse model, observing a depolarization of the mitochondrial membrane.[96] In *Helianthus tuberosus* L. the novel sesquiterpene lactone furanoheliangolide showed a much lower level of bioactivity against *T. cruzi*. [97]

Ambrosia is another important genus of the Asteraceae family with several species with trypanocidal potential, which in the last 15 years has been exhaustively studied by Dr. VP Sülsen's group in Argentina. Psilostachyin, a natural sesquiterpene lactone, isolated from *A. tenuifolia* Spreng., was evaluated on the growth, proliferation and viability of epimastigotes, observing that the effect on parasite growth was irreversible (> 1.0 µg/mL concentration).[98] Psilostachyin C, isolated from *A. scabra* Hook. & Arn., was *in vitro* evaluated against epimastogotes, trypomastigotes and amastigotes, observing an IC_{50}=0.6, 3.5 and 0.9 µg/mL, respectively, and in *in vivo* assay, also exerted an inhibitory effect against *T. cruzi* with significative reduction of parasitemia.[99] In *A. elatior* L. only the sesquiterpene lactone cumanin and in *A. scabra* the sesquiterpene lactones, cumanin and cordilin were active against epimastigotes and trypomastigotes with IC_{50} = 12 and 26 µM, respectively.[100] Both species, *A. elatior* and *A. scabra* were collected in Buenos Aires-Argentina. Psilostachyin and psilostachyin C, isolated from *A. tenuifolia* and *A. scabra*, respectively, were evaluated for their interaction with hemin, observing that both sesquiterpene lactones induced parasite death by apoptosis, and the increase in the generation of reactive oxygen species (ROS) in epimastigotes.[101]

In *Smallanthus sonchifolius* (Poepp.) H. Rob., native from the Andean of South America, collected in Tucuman-Argentina, the germacranolide-type sesquiterpene lactones, enhydrin (1), uvedalin (2), and polymatin B (3), showed activity against epimastigotes with IC_{50} = 0.84, 1.09, and 4.90 μM, respectively, and the compounds 1 and 2 showed IC_{50}=33.4 and 25.0μM, respectively, against trypomastigotes.[6] These same compounds, isolated from *S. sonchifolius*, collected in the Centro Universitario "Horco Molle", University of Tucumán-Argentina, were also evaluated on *T. cruzi*, observing that the three compounds exhibited activity on epimastigotes

(IC_{50} = 0.35-0.60 µg/mL).[102] An inseparable mixture of two new trixikingolides from *Trixis vauthieri* DC. showed activity (IC_{50} = 0.053 µM) against trypomastigotes and amastigotes, 70 times more potent than benznidazole.[103]

Extract of aerial parts of *Aristeguietia glutinosa*, collected in "Pangor" plateau, Quito-Ecuador, showed activity against epimastigotes (IC_{50} = 19.6 µg/mL) while los diterpenoids, (+)-15-hydroxy-labd-7-en-17-al (1) and (+)-13,14,15,16-tetranor-labd-7-en-17,12-olide (2), were more active with IC_{50}=3.0 and 15.6 µg/mL, respectively.[104] Likewise, showed activity against trypomastigotes and the secondary metabolites 1 and 2 were the most active components with 91±4% and 54±7% of lysis, respectively.[105] EO from *Phania matricarioides* (Spreng.) Griseb., with lavandulyl acetate (40.1%) as the major component, displayed activity against *T. cruzi* (IC_{50}=2.2 µg/mL).[106]

On the other hand, thirty-six terpenes were isolated from Asteraceae plants from arid lands and evaluated against *T. cruzi* showing a sensitivity of 33% of active compounds.[107] Likewise, extracts from 13 Argentinean Asteraceae species were evaluated against epimastigotes, showing that DCM extracts of *Aspilia silphioides* (Hook. & Arn.) Benth. & Hook. f., *Viguiera tuberosa* Griseb., *Verbesina subcordata* DC., *Gimnocoronis spilanthoides* (D. Don ex Hook. & Arn.) DC., *Gaillardia megapotamica* (Spreng.) Baker, *Thelesperma megapotamicum* (Spreng.) Herter and *Zexmenia buphtalmiflora* (Lorentz) Arisa showed trypanocidal activity (inhibitions higher than 60% at 10 µg/mL), and the MeOH extracts of *Helenium radiatum* (Less.) Seckt. and *G. megapotamica* (inhibitions of 70.1 and 77.7%, respectively, at 10 µg/mL).[108]

Table 1 - List of American families and species, including Peruvian species and species of regional floras, used in tests on trypanocidal activity, emphasizing the genera of Peruvian species

N.º	Peruvian families	American Species Tested	Genera of Peruvian Species
1	Winteraceae [1] 1	*Drimys brasilienses*	*Drimys* 1
2	Piperaceae [3] 811(528)	*Peperomia pseudopereskiifolia*, *Piper aduncum*, *P. jacquemontianum*, *P. jericoense*, *P. lacunosum*, *P. malacophyllum*, *P. regnellii* var. *pallescens*, *P. solmsianum*, *P. tecnoiifolium*, *P. tuberculatum*	*Peperomia* (381/226) *Piper* (429/302)
3	Aristolochiaceae [1] 40(16)	*Aristolochia cymbifera*	*Aristolochia* (40/16)
4	Annonaceae [23] 193(41)	*Annona crassiflora*, *A. coriaceae*	*Annona* (19/4)
5	Siparunaceae (= Monimiaceae) [2] 55(14)	*Siparuna sessiflora*	*Siparuna* (40/10)
6	Lauraceae [15] 197(49)	*Aniba panurensis*, *A. parviflora*, *A. rosaedera*, *Nectandra leucantha*, *N. megapotamica*, *N. oppositifolia*, *Ocotea cymbarum*	*Aniba* 16 *Nectandra* (29/5) *Ocotea* (62/22)
7	Arecaceae [33] 145(19)	*Syagrus coronata*	*Syagrus* (2/1)
8	Poaceae [150(1)] 719(112)	*Cymbopogon citratus*	*Cymbopogon* 1
9	Berberidaceae [1] 32(18)	*Berberis microphylla*	*Berberis* (32/8)
10	Fabaceae [138(1)] 971(280)	*Haematoxylum brasiletto*, *Vatairea macrocarpa*	*Vatairea* 3
11	Rosaceae	*Kageneckia oblonga*	*Kageneckia* 1

	[24] 120(12)		
12	Connaraceae [3] 17(4)	*Connarus suberosus*	*Connarus* (7/2)
13	Calophyllaceae = Clusiaceae	*Calophyllum brasiliense*, *Mammea americana*	*Calophyllum* 2 *Mammea* 1
14	Clusiaceae [21] 124(28)	*Clusia studartiana*, *Rheedia longifolia*	*Clusia* (40/11) *Rheedia* 3
15	Malpighiaceae [19] 134(26)	*Malpighia glabra*	*Malpighia* 3
16	Salicaceae [2] 4 = Flacourtiaceae [18] 63(8)	*Casearia sylvestris*	*Casearia* (19/3)
17	Euphorbiaceae [57] 305(88)	*Croton heliotropiifolius*	*Croton* (49/31)
18	Vochysiaceae [4] 31(2)	*Qualea grandiflora*	*Qualea* (9/2)
19	Myrtaceae [20] 160(52)	*Blepharocalyx salicifolius*, *Eugenia brejoensis*, *E. uniflora*, *Psidium laruotteanum*	*Blepharocalyx* 1 *Eugenia* (51/20) *Psidium* (8/3)
20	Melastomataceae [42] 637(230)	*Monochaetum myrtoideum*	*Monochaetum* (4/1)
21	Anacardiaceae [12] 32(6)	*Schinus mole*	*Schinus* 4
22	Rutaceae [25(1)] 67(10)	*Ruta graveolens*, *Zanthoxylum chiloperone* var. *angustifolium*	*Ruta* 2, *Zanthoxylum* (17/4)
23	Meliaceae [10] 69(4)	*Trichilia havanensis*	*Trichilia* (27/2)

24	Sapindaceae [20(1)] 180(43)	*Sapindus saponaria*	*Sapindus* 1
25	Malvaceae [35] 256(82)	*Luehea ochrophylla*	-
26	Primulaceae [4] (Myrsinaceae) [9] 72(23)	*Myrsine guianensis*	*Myrsine* (22/13)
27	Clethraceae	*Clethra fimbriata*	*Clethra* (11/3)
28	Boraginaceae [16] 131(36)	*Bourreria huanita*	-
29	Solanaceae [42] 538(162)	*Acnistus arborescens*, *Aureliana fasciculata* var. *fasciculata*, *Fabiana imbricata*	*Acnistus* 1 *Fabiana* 1
30	Bignoniaceae [47] 166(13)	*Crescentia cujete*, *Handroanthus impetiginosus*	*Crescentia* 2 *Handroanthus* 12
31	Lamiaceae [20] 190(71)	*Hyptis pectinata*, *Hypenia salzmanni*, *Marrubium vulgare*, *Rhaphiodon echinus*	*Hyptis* (27/2) *Marrubium* 1
32	Verbenaceae [23] 200(44)	*Lippia alba*, *L. citriodora L. dulcis*, *L. macrophylla*, *L. micromera*, *L. origanoides*, *L. sidoides*	*Lippia* (12/4)
33	Asteraceae [222(14)] 1432(729)	*Achillea ptarmica* *Acmellea bellidioides* *Ageratina vacciniaefolia* *Ageratum conyzoides* *A. fastigiatum* *Aldama discolor* (syn. *Viguiera discolor*) *Ambrosia elatior* *A. scabra* *A. tenuifolia*	*Achillea* 1 *Ageratina* (40/24) *Ageratum* 2 *Ambrosia* (6/2) *Aristeguieta* (11/9) *Artemisia* 2 *Baccharis* (70/20) *Calea* (6/1) *Elephantopus* 2

		Anacyclus pyrethrum *Anthemis nobilis* *A. auriculata* *Aristeguietia glutinosa* *Artemisia annua* *A. campestris* *A. copa* *A. herba-alba* *Aspilia silphioides* *Baccharis dracunculifolia* *B. punctulata* *B. retusa* *B. sphenophylla*, *B. spicata* *B. uncinella* *Calea pinnatifida* *C. uniflora* *Calyptocarpus biaristatus* *Castanedia santamarcensis* *Cynara scolymus* *Decachaeta incompta*, *Elephantopus mollis*, *Flourensia oolepis* *Gaillardia megapotamica*, *Gochnatia pulcra* *Gymnocoronis spilanthoides* *Helenium radiatum* *Helianthus tuberosus*	*Flourensia* (5/5) *Gochnatia* (4/3), *Gymnocoronis* 1, *Helenium* 1 *Helianthus* 1 *Helichrysum* 1 *Mikania* (82/18) *Pentacalia* (30/21) *Pluchea* (4/2) *Porophyllum* (1) *Schkuhria* (2) *Smallanthus* (7/1) *Stevia* (24/15) *Tanacetum* 3 *Tessaria* 1 *Trixis* 6(2) *Verbesina* 41(21) *Vernonia* (39/20) *Viguiera* 37(10)

		Helichrysum italicum *Hyalis argentea* *Inula viscosa* *Mikania braziliensis* *M. micrantha* *M. parodii* *M. periplocifolia* *M. variifolia* *Parthenium hysterophorus*, *Pentacalia desiderabilis* *Phania matricarioides* *Pluchea carolinensis* *Podanthus ovatifolius* *Porophyllum ruderale* *Smallanthus sonchifolius* *Sphagneticola trilobata* *Stevia alpina* *S. gilliesii* *S. maimarensis* *S. satureifolia* *S. satureiifolia* var. *satureiifolia* *Tanacetum vulgare* *T. parthenium* *T. sombolii* *Tessaria absinthioides* *Thelesperma megapotamicum* *Tithonia diversifolia* *Trixis vauthieri*	

		Urolepis hecatantha *Verbesina subcordata* *Vernonanthura nebularum* *Vernonia brasiliana* *V. liatroides* *V. plantaginoides* *V. polyanthes* *V. scorpioides* *Viguiera anchusaefolia* *V. tuberosa* *Zexmenia buphtalmiflora*	
34	Apiaceae [29(1)] 88(26)	*Crithmum maritimum*	-

Legend: [X(X)]; X(X) = [Number of genera (Endemic genera)] Number of species (Endemic species); Genus (X/X) = Genus (Number of species/Endemic species). The underlined genera are American, but have not been reported for the flora of Peru.

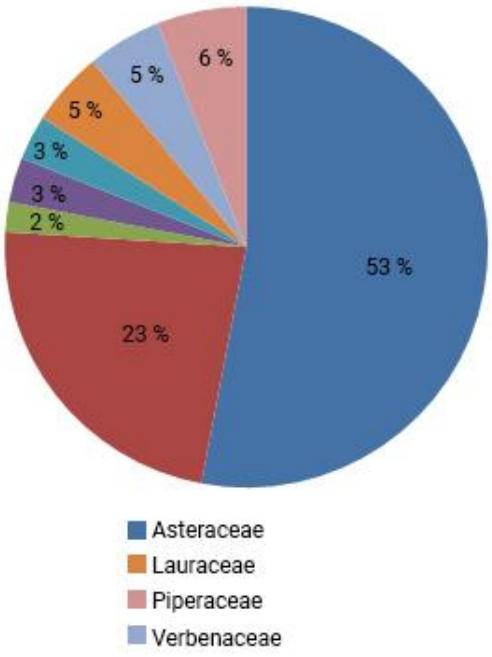
Source: Taken from Brako & Zarucchi.[15]

Trypanocidal activity of regional flora species

Plant species evaluations have also been carried out in regional floras of Central and South American, El Salvador, Colombia, Brazilian Cerrado and Brazilian Caatinga, Chile and Mexico, being distributed in very specific ecological environments. These species belonged to the families Boraginaceae (1), Melastomataceae (1) and Solanaceae (1), from Central and South American region.[109] Meliaceae (1) and Piperaceae (3) from Salvadoran flora.[110] Bignoniaceae (1), Clusiaceae (2), Malpighiaceae (1), Piperaceae (2) and Solanaceae (1), from Brazilian biodiversity.[111] Connaraceae (1), Fabaceae (1), Myrtaceae (2) and Primulaceae (1), from Brazilian Cerrado.[112] Asteraceae (1), Clethraceae (1) and Siparunaceae (1), from Colombian flora.[113] Asteraceae (1), Bignoniaceae (1) and Rutaceae (1), from Minas Gerais.[114] Asteraceae (1), Berberidaceae (1), Rosaceae (1) and Winteraceae (1), from Central Chile (Maule

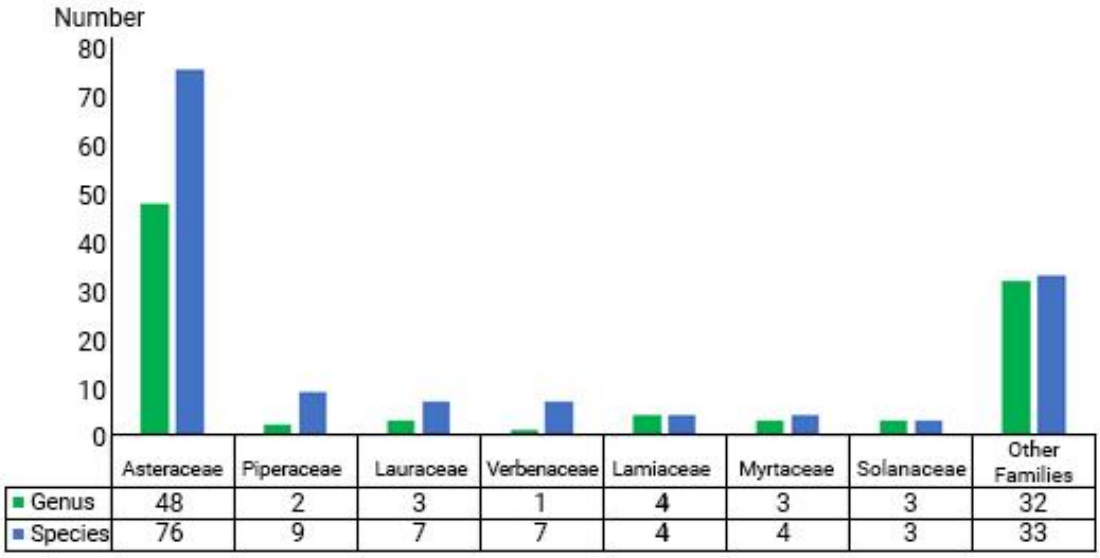
Region).[115] Anacardiaceae (1), Fabaceae (1), Lamiaceae (1) and Poaceae (1), from Nuevo León-Mexico.[116] Likewise, Arecaceae (1), Lamiaceae (2), Myrtaceae (1) y Verbenaceae (1), from Brazilian Caatinga.[117]

Figures 2 and 3 shows the percentage of number of species per family, and number of genera and species among the most representative families, respectively, in 34 families of phanerogams and families of regional floras, tested against *T. cruzi*.



Source: Own elaboration.

Fig. 2 – Percentage of number of species per family in 34 families of American phanerogams, including Peruvian species, indicated in table 1 and supplemented with species from regional floras, tested against *T. cruzi*., other families 23.



	Asteraceae	Piperaceae	Lauraceae	Verbenaceae	Lamiaceae	Myrtaceae	Solanaceae	Other Families
Genus	48	2	3	1	4	3	3	32
Species	76	9	7	7	4	4	3	33

Source: Own elaboration.

Fig. 3 – Number of genera and species in 34 families of American phanerogams, including Peruvian species, indicated in table 1 and supplemented with species from regional floras, tested against *T. cruzi*.

Peruvian plants species

A recent report on Biodiversity in Peru revealed that the vascular flora in Peru is made up of 19,147 species, of which 7,590 are endemic.[118] On this significant number of plant species, although there are some important ethnobotanical studies in traditional medicine,[119,120] there are few studies that relate them to phytochemistry and biological activity. The coronavirus pandemic, however, has sparked interest in using Peruvian plant species in the home treatment of this disease [121,122,123]

There is a very significant number of families, genera and species reported for the Flora of Peru (table 1) used in other countries, in the treatment of trypanosomiasis. This is the case of the Piperaceae family with 381 species of *Peperomia* and 429 species of *Piper* and a high degree of endemism (226 and 302 species, respectively). Another notable example corresponds to the families Annonaceae (*Annona* with 19 species), Siparunaceae (*Siparuna* with 40 species) and Lauraceae (*Nectandra* and *Ocotea* with 29 and 62 species, respectively). However, the Asteraceae family with 82, 70 and 41, species of the *Mikania*, *Baccharis* and *Verbesina* genera, respectively, are the ones that exhibit the greatest potential. In

recent years, 230 new species of Asteraceae have been added to the flora of Peru, as well as 29 new genera.[16]

A special mention corresponds to the species *Sapindus saponaria*, a species from the seasonally dry tropical forest of northern Peru[51] and *Mammea americana*, a delicious native fruit tree, also from the north coast of Peru,[43,44] have been shown to have an important source of secondary metabolites in the treatment of trypanosomiasis.

For all this, the plant species that constitute the Flora of Peru is an unlimited source of secondary metabolites, potentially useful in the treatment of trypanosomiasis in Peru, America and the world.

Conclusions

The growing resistance of pathogens to conventional drugs, the side effects of these drugs in long-term treatments and the effect of Climate Change, which can induce mutations that increase the aggressiveness of pathogens, lead to exploring other sources of drugs. A primary source of these drugs are extracts obtained from plants. As mentioned in this study, extracts and isolated compounds from numerous genera and species of the Asteraceae family have shown promise in the treatment of Chagas disease. These compounds were mostly isolated from essential oils and belong to the group of sequiterpene lactones. In this scenario, the plant species of the Peruvian flora, especially those that make up the Asteraceae family, constitute a promising research source available to national and foreign researchers.

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Conflict of interests

The authors declare that there is no conflict of interest.