The anti-Trypanosoma activities of medicinal plants: A systematic review of the literature

Shahin Nekoei1 | Faham Khamesipour1,2 | Solomon Habtemariam3 | Wanderley de Souza4,5 | Pardis Mohammadi Pour6 | Seyed Reza Hosseini1

1Faculty of Veterinary Medicine, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran
2Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Iran
3Pharmacognosy Research Laboratories and Herbal Analysis Services, University of Greenwich, Central Avenue, Chatham-Maritime, Gillingham, Kent, UK
4Laboratório de Ultraestrutura Celular Hertha Meyer, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
5Instituto Nacional de Ciência e Tecnologia em Biologia Estrutural e Bioimagens e Centro Nacional de Biologia Estrutural e Bioimagens, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
6Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: The existing drug treatments for trypanosomiases are limited and suffer from shortcomings due to their toxicity and the emergence of resistant parasites. Developing anti-trypanosomal compounds based on natural products is a promising way of fighting trypanosomiases.

Objectives: This study aims to identify through scientific review a large variety of medicinal plants (anti-trypanosomal) used worldwide and scientifically shown to display anti-trypanosomal effects.

Methods: To collect data, the anti-trypanosomal activities of Africa, Asia, the Middle East, South America, North America, Europe and Oceania medicinal plants have been checked by considering the published paper.

Results: Based on collected data, 77 natural molecules were reported in the literature. Of which 59 were from the African region, 11 from Asia, 3 from Europe and 4 from Latin America. These active components belong to alkaloids, triterpenoids, lactone, quinoids, flavonoids, iridoids, lignans, steroids, lipids, oxygenated heterocycles, benzenoids, proteins, coumarins, phenylpropanoids and peptides. We also specified the prosperous plants with unique anti-trypanosomal activities.

Conclusions: However, there is a need for further studies on the ability of the isolated compounds to ameliorate the trypanosome-induced pathological alterations and also the elucidation of their modes of actions and activities against other trypanosome species.

KEYWORDS
anti-trypanosomal activity, medicinal plants, review

INTRODUCTION

Trypanosomiases are a widespread vector-borne disease globally that affects humans and domestic and wild animals. The pathophysiology of these diseases may vary depending on the pathogenic species involved and the host. Its symptoms in humans include irregular fever and septicemia. At the same time, in animals, a decrease in the number of red blood cells and body mass can lead to unproductivity and death (Osório et al., 2008). Trypanosomiases have been considered a significant public health problem in animals and humans (Hassan et al., 2020).

The global prevalence of trypanosomiases, in general, is underreported (Wilkinson and Kelly, 2009). The two significant trypanosomiases in humans are the African Trypanosomiases (HAT, also known
as sleeping sickness) and Chagas disease, caused by Trypanosoma brucei and Trypanosoma cruzi. According to the World Health Organization (PAHO, 2016) data, T. cruzi infects about 5–6 million people worldwide and causes approximately 10,000 deaths per year (WHO, 2015). For HAT, its incidence is now at a historic low, with fewer than 1000 cases reported in 2018 (WHO, 2018).

A small number of trypanocidal drugs have shown efficacy against the two species of parasites. These include two approved drugs that can treat Chagas Disease during its acute phase (Benznidazole and Nifurtimox) (Sepúlveda-Robles et al., 2019). The recommended drugs to treat the HAT include suramin (EC: 205-658-4), pentamidine (EC: 205-424-1), melarsoprol (EC: 207-793-4) and Fexinidazole Winthrop (Dickie et al., 2020). Fexinidazole is a DNA synthesis inhibitor for the Neglected Diseases initiative (DNDi) for the oral treatment of HAT and Chagas’ disease, which shows activity against Trypanosoma brucei gambiense and T. b. rhodesiense as well as preceeds through Phase II clinical trial based on FDA definition (Deeks, 2019). The other drugs, including Nifurtimox, are in Phase III clinical trials, and Eflornithine (EC: 205-658-4) has not yet entered into clinical trial stages. However, the first three drugs have limitations, including poor efficacy, potential adverse effects and the development of resistance by the parasites (Wilkinson and Kelly, 2009). Oral fexinidazole is a valuable first-line treatment option in the early stages of (stage 1 or early stage 2) African Trypanosoma brucei gambiense (Kande Betu Ku Mesu et al., 2021). Eflornithine is a standard treatment for second-stage therapy, and nifurtimox-eflornithine combination therapy is a proper combination for first-line use in HAT control programs (Priotto et al., 2009). Additionally, DNDi has developed another oral therapy, acoziborole, suitable for the treatment of both stage 1 and stage 2 disease in a single dose (Dickie et al., 2020).

Also, the neglected disease status means a little economic benefit for developing novel drugs in this field (Dickie et al., 2020). There is little interest in developing drugs against these diseases because they are neglected. However, they are called ‘neglected diseases’ because pharmaceutical companies have little interest in investing in them, as fexinidazole has recently met that need for T. brucei gambiense (Kande Betu Ku Mesu et al., 2021). However, melarsoprol is very toxic and is still being used against T. brucei rhodesiense (Fairlamb and Horn, 2018), and resistance may still arise against fexinidazole, so new lead compounds for drugs against these parasites remain essential. Thus, there has been a considerable need to find new trypanocidal agents with better efficacy and safety profiles.

Natural products are valuable sources for discovering and developing effective medicines against various diseases (Hashemi et al., 2021; Newman and Cragg, 2016; Nezaratzade et al., 2021; Tajbakhsh et al., 2021a; Tajbakhsh et al., 2021b). The WHO report highlighted that a quarter of currently useful drugs had been derived from traditional plants. For many parts of the world, especially where trypanosomiasis are prevalent in Africa, India, China, the Middle East and South Asia, traditional medicines with local preparations are the predominant means of therapy (Ahmad Khan and Ahmad, 2019). These countries are also endowed with tremendous medicinal plant resources, some of which have shown efficacy under in vitro and/or in vivo conditions. At present, the available reviews in this field report anti-trypanosomal activity for particular regions, such as the African region (Ibrahim et al., 2014; Lawal et al., 2015), Myanmar (Asia) (Bawm, 2010) and Saudi Arabia (Al-Musayeib et al., 2012). These exciting but somehow dated but interesting publications reported a lot of medicinal plants and some isolated active compounds. Finally, the current, up-to-date review covers natural products isolated from plants used worldwide and active against trypanosomiasis.

### 1.1 Ethnopharmacology of anti-trypanosomal medicinal plants in Africa continent

Since the primitive period, herbs have been a valuable source of medication for both human and livestock diseases (Odhiambo et al., 2011). During these thousand years of observation, it has been found that different parts of herbs possess healing properties. With the advancement in pharmaceutical and medical sciences, phytoconstituents were subsequently confirmed to be accountable for the curative characteristics of plants. Nowadays, high-tech methods have resulted in the isolation and elucidation of these phytoconstituents. Some of these phytoconstituents have served as lead compounds to develop chemotherapeutic drugs against diseases, whether infectious or non-infectious (Kasilo et al., 2010).

On the one hand, some modern drugs have their ethnopharmacological sources. Nevertheless, despite technological advances, the discovery of new drugs faces a primary innovation deficit that unfavourably impacts the pharmaceutical industry. On the other hand, current studies demonstrate that entry barriers have decreased for introducing a new drug (DiMasi & Paquette, 2004; Patwardhan, 2005). Seventy-five per cent of the approved anti-infectious disease drugs from 1981 to 2002 are natural origins (Newman et al., 2003), while 61% of all new chemical compounds presented as drugs during the same period could be considered natural products (Gupta et al., 2005).

Aside from this significant role of medicinal herbs in drug discovery, the use of local herbal products provides the only option for therapeutic purposes for African populations. The primary reason for this issue is the lack of a sound health care system in some parts of the continent, which causes the population’s vulnerability to many infectious diseases (Elujoba et al., 2005). Eighty per cent of the African population depends almost entirely on herbal medicinal products for their primitive health care needs (Kasilo et al., 2010).

One of the significant infections that severely affect humans and animals in Africa is African trypanosomiasis, also called ‘sleeping sickness’ in humans or ‘Nagana’ in animals. (Atawodi 2005; Welburn et al., 2009). It is one of the most neglected parasitic diseases that affect human health and dramatically reduces Africa’s livestock productivity (Atawodi 2005; Welburn et al., 2009). Preliminary estimates show that almost 70 million people distributed over 1.55 million km² in Africa are at risk of this infectious disease (Simarro et al., 2012). In addition, animal trypanosomiasis, or Nagana, are distributed over nearly 25 million...
km² in Africa, where livestock productivity fell by 50%. The important species in this disease include *Trypanosoma vivax*, *Trypanosoma congoense*, *Trypanosoma evansi* and *Trypanosoma brucei* (Mbaya et al., 2009). Currently, the African trypanosomiasises chemotherapy remains abandoned due to the available approved drugs with some concerns, including parasite resistance, toxicity, poor availability, high cost and parenteral root of administration (Ibrahim et al., 2014). Fortunately, the continent has vast resources of medicinal plants that are traditionally used to cure this disease. This is evident in the tendency to use ethnobotanical science to manage disease in different parts of Africa (Atawodi et al., 2002; Ntie-Kang et al., 2013). It is important to note that studies have confirmed the impact of these African herbal remedies as anti-trypanosomal agents under in vitro and/or in vivo models. Hence, a critical review of these studies (anti-trypanosomal) African medicinal plants in the African continent and anti-trypanosomal plants in other continents is required to provide a comprehensive record to specify gaps in knowledge about the basic strategies to address such gaps.

### 2 | MATERIALS AND METHODS

#### 2.1 | Search strategy

Literature about medicinal plants (with anti-trypanosomal activity) was collected online from published articles using the keywords: 'Trypanosoma AND medicinal plant; 'Trypanosoma AND natural product' from 1960 to May 2020. These keywords were entered into the primary scientific databases, such as PubMed, Science Direct, Scopus and Google scholar. The articles obtained were included based on the reliability of their source. Some articles were found by examining the bibliography of other publications or by directly accessing the webpage of the journal.

#### 2.2 | Inclusion and exclusion criteria

The documents used were selected based on several criteria: (a) they have published articles or doctoral theses, (b) research has been carried out on antiparasitic medicinal plants in general and anti-trypanosomal plants in particular, (c) mention at least the minimum inhibitory concentration or the inhibition degree of the extract(s) or isolated compound(s) considering the anti-trypanosomal activity, (d) in cases where different authors present results for the same plants, the most recent results are prioritised unless they present more minor details such as cytotoxicity tests, (e) due to the volume of data available for African region medicinal plants, only plants whose bioactive compound have been isolated were reported herein. The EC50 below 25 μM or μg for pure compounds was considered the search limit for the whole region. The author aimed to review the tested medicinal plant extracts, not just the isolated compounds from plants. Literature was not used when the results came from an ethnobotanical survey without scientific investigation.

#### 2.3 | Data extraction

The information such as the species and family of the plant, the type of extraction, the active compound(s) if isolated, the strain of *Trypanosoma* tested, the 50% effective concentration and cytotoxic concentration, country of study and the name of the author were extracted from relevant literature and presented in the form of a table according to geographical location.

#### 2.4 | Ethical approval statement

An ethics statement is not applicable because this study is based exclusively on published literature.

### 3 | RESULTS AND DISCUSSION

#### 3.1 | Analysis of the included literature

A total of 70 articles have been selected based on the inclusion criteria. Twenty studies reported African anti-trypanosomal plants, 11 reported Asian anti-trypanosomal plants, three reported the Middle East anti-trypanosomal plants and 15 reported Latin American anti-trypanosomal plants. Two studies reported North American anti-trypanosomal plants, and nine studies reported European anti-trypanosomal plants. One study reported Oceania’s anti-trypanosomal plants (Figure 1). A total of 70 relevant kinds of literature have been selected based on the inclusion criteria. The PRISMA 2020 flow diagram shows 25, 16, 18, 1, 9 and 1, including database searches (Figure 2) (Page et al., 2021).

#### 3.2 | African region plants

Ethnobotanical resources for Africa demonstrated unusual plants with anti-trypanosomal activity (Ibrahim et al., 2014; Lawal et al., 2015). We explained 264 and 215 plants, respectively, which were assessed for anti-trypanosomal activity. Due to the high amount of data available for African region anti-trypanosomal plants, only the plants with the minimum inhibitory concentration of the bioactive compound were scrutinised (Table 1 and Figure 3).

More than 200 investigated plants (Ibrahim et al., 2014; Lawal et al., 2015) show potential trypanocidal activity; only 34 plants have their active compounds isolated in pure form. Only their compounds (flavonoid, saponins, alkaloid etc.) are reported for the other plants. This is due to the lack of resources in Africa to isolate the active molecules. Among these 34 plants, just six have been investigated in vivo. The anti-trypanosomal activity of the extracts was most assessed on *Trypanosoma brucei* subspecies, which are responsible for African trypanosomiasises (WHO, 2015). Considering the importance of trypanosomiasises caused by this species in Africa, the development of...
| Scientific name                  | Family               | Part(s) used                      | Solvent | Bioactive compound(s)                                                                 | Model      | Sub species | cytotoxic/biological activity | EC50          | Country                 | References                  |
|----------------------------------|----------------------|-----------------------------------|---------|--------------------------------------------------------------------------------------|------------|-------------|------------------------------|--------------------------|---------------------------|-----------------------------|
| Abrus precatorius L.             | Leguminosae          | Leaf                              | Methanol| Abruquinone K, L, A and D                                                            | In vitro   | T. b. r     | 57.3, 7.5, 34.5 and 4.8 μM   | 0.1, 0.02, 0.02 and 0.01 μM | South Africa            | (Hata et al., 2014)          |
| Aframomum letestuanum            | Zingiberaceae        | Seed                              | DCM     | Letestuianin C and 5-hydroxy-1,7-bis(4-hydroxyphe-no)-hepta-4,6-dien-3-one           | In vitro   | T. b. b     | -                           | 1.4 and 2.6 μg/ml          | Cameroon                 | (Kamnaing et al., 2003)     |
| Allexis cauliflora (Oliv.) Pierre| Violaceae            | Leaf                              | DCM     | 22-Hydroxycleroster                                                                  | In vitro   | T. b. b     | 1.12 μM                      | 1.56 μM inhibit the glycolytic enzyme PGI | Cameroon                 | (Nganso et al., 2011)        |
| Ancistrocladus abbreviatus subsp.| Ancistrocladaceae    | Leaves, stem bark and roots       | DCM     | Ancistrocladin, Ancistrotanazinines B and C, Ancistructose A and O.N-dimethyl- | In vitro   | T. b. r/Tc | 28.3, 8.1, 40.7, 6.5 and 42.9 μg/ml | 0.17 to 12.41 μM          | Cameroon                 | (Simoben et al., 2018)       |
|                                    |                      |                                   |         | ancistrocladidine, Ancistrotanzanine D and E, Ancistrotectorline A and O.N-dimethyl- |            |             |                              |                          |             | (Bringmann et al., 2003, Bringmann et al. 2004) |
| Solanecio angulatus              | Fabaceae             | Flower, twig, leaf                | methanol| Artemisinin                                                                          | In vitro   | T. b. b     | >500                         | 27.39 12.17e, 12.47e μg/ml | Tanzania                | (Nibret et al., 2009)       |
| Cotula phillipsiae Arctania annua| Asteraceae           |                                    | P.E.    | Isotricetin, Isosinus, Isosinon, Isosinon-8, Isosinon-12, Isosinon-13, and           | In vitro   | T. b. r     | 15.6 μg/ml                    | 6.9, 10.6 12.5 and 25 μg/ml | Nigeria                 | (Nweze, Anene and Asuzu, 2011) |
| Buchholzia coriacea              | Capparaceae          | Seeds                             | Methanol| Beta-sitosterol α-sulphur                                                           | In vitro   | T. b. b     | No noticeable morphological changes | 12.5 and 25 μg/ml          | Nigeria                 | (Simoben et al., 2018)       |
| Cassytha filiformis L.           | Lauraceae            | Leaf                              | DCM     | Cassythine                                                                            | In vitro   | T. b. b     | 15.2 μM                      | 6 μM                     | Cameroon                 | (Simoben et al., 2018)       |
| Chrysanthemum cinerariifolium    | Asteraceae           | Flowers                           | n-hexane| Cinerin (II), Pyrethrins (I, II), Jasminol (II)                                       | In vitro   | T. b. r     | 28.6, 95.1 and 31.5          | 12.2 6.9, 10.6 12 μg/ml   | South Africa            | (Hata et al., 2011)          |
| Cussoria zimmermannii            | Araliaceae           | Root bark                         | Petroleum ether extract | Polyaeyetolines (MS-1, MS-2 and MS-4)                                               | In vitro   | T. b. r/Tc | 54(17), 12(3.6) and 58(22) μM (μg/ml) | 18(5.4), 0.46 (0.14) and 1.0(0.42) 26(7.9), 0.65 (0.20) and 0.40 (0.15) μM (μg/ml) | Tanzania                | (Sennet et al., 2007)       |
| Dioncophyllum thollonii           | Dioncophyllaceae     | Roots                             | DCM     | Dioncophylline E                                                                     | In vitro   | T. b. r/Tc | -                            | 0.73 and 18.4 μg/ml       | Cameroon                 | (Simoben et al., 2018)       |
| Drypetes gerardii Hutch.          | Putranjivaceae       | Stem                              | DCM/methanol| Putranoside A                                                                       | In vitro   | T. b. r     | 68.2 μM                      | 18.0 μM                  | South Africa            | (Hata et al., 2014)          |
| Entada abyssinica                 | Leguminosae          | Stem                              | Ethanol | Kolavenol                                                                            | In vitro   | T. b. r     | -                            | 2.5 mg/ml (8.6 mM)        | Tanzania                | (Freiburghaus et al., 1998)  |

(Continues)
| Scientific name                  | Family                  | Part(s) used | Solvent          | Bioactive compound(s)                          | Model       | Sub species | cytotoxic/biological activity | EC50 | Country       | References                           |
|---------------------------------|-------------------------|--------------|------------------|------------------------------------------------|-------------|-------------|-------------------------------|------|---------------|--------------------------------------|
| Eucalyptus maculata Hook.       | Myrtaceae               | Leaf         | Hexane, ethyl acetate and methanol | Triterpenoid (β,β,13,β-dihydroxy-urs-11-en-28-oic acid) | In-vitro    | T. strains s427 WT, B48 and AQP2/3KO | 1.58 μg/ml, 1.58, 1.55 and 1.39 μg/ml | Nigeria | (Ebiloma et al., 2017) |
| Garcinia lucida Vesque          | Clusiaceae              | Stem         | DCM              | Dihydrochelery-thrine, 6-acetonyl-dihydrochelery-thrine, Lucidamine A | In-vitro    | T. b. | 35.4, 15.3 and 11.6 μM | 0.8, 3.9 and 14.1 μM | Cameroon | (Fotie et al., 2007) |
| Keetia leucantha (K.Krause) Bridson | Rubiaceae              | Leaf         | DCM              | Oleanolic acid/ursolic acid/betulinic acid/β-ionone | In-vitro    | T. b.b | -                            | 7.3, 2.5, 19.1, 10.5 μg/ml | Nigeria | (Bero et al., 2013) |
| Khaya anthotheca (Welw.) C.D.C. | Meliaceae               | Seeds        | Pet. ether       | Grandifolione | In-vitro | T.b.r/T.cr | 44.7                            | 10.6/6/20.9 μg/ml | Uganda | (Oboh, Lawal and Malan, 2013) |
| Mitracarpus scaber Zucc. ex Schult. & Schult. | Rubiaceae              | Leaf         | Methanol         | Azaantha-quinone | Invitro/invivo | T.c.o in bloodstream of BalbC mice, 50 mg/kg/d | Inhibit reduced coenzyme Q1-dependent O2 | 50 μg/ml | Nigeria | (Nok, 2002) |
| Morinda lucida Benth.           | Rubiaceae               | Leaves       | Methanol         | β-sitosterol | In-vitro | T. b | 100                            | 12.5 μg/ml | Nigeria | (Nweze, 2012) |
| Ocimum gratissimum L.           | Lamiaceae               | Seed oil     | Oil              | Myrcen, Limonen and Citronellal | In-vitro | T. b | >50, >50 and >50 μg/ml | 2.24, 4.24 and 2.76 μg/ml | Benin | (Kpadonou Kpovissi et al., 2014) |
| Polyalthia longifolia (Sonn.) Thwaites | Annonaceae             | Leaf         | Hexane, ethyl acetate and methanol | Clerodane | In-vitro | T.c.o | -                             | 0.38 μg/ml | Nigeria | (Ebiloma et al., 2017) |
| Polyalthia suaveolens Engl. & Diels | Annonaceae             | Leaf         | DCM              | Mixture of polysin and greenwayodendrin-3-one | In-vitro | T.b.b | 170 μM                           | 18 μM | Cameroon | (Simoenen et al., 2018) |
| Schkuhria pinnata (Lam.) Kurz ex Thell. | Asteraceae             | Whole plant  | DCM/methanol     | Schkuhrin I and II | In-vitro | T.b., T.cr | 5.26 and 9.03 μM | 0.9 and 1.5 μM/16.4 and 26.9 μM | South Africa | (Mokoka et al., 2013) |
| Strychnos spinosa Lam.          | Loganiaceae             | Leaf         | Ipophilic        | Saringosterol, 24-hydroperoxy-24-vinylcholesterol | In-vitro | T.b.b | >233.3 and 16.4 μM | 7.8 and 3.2 μM | Tanzania | (Hoet et al., 2007) |

(Continues)
| Scientific name                  | Family           | Part(s) used | Solvent    | Bioactive compound(s)                                                                 | Model   | Sub species | cytotoxic/biological activity | EC50     | Country    | References                  |
|---------------------------------|------------------|--------------|------------|--------------------------------------------------------------------------------------|---------|-------------|--------------------------------|----------|-----------|----------------------------|
| *Teclea trichocarpa* (Engl.)    | Rutaceae         | Leaves       | Methanol   | Melicopicine, skimmianine and α-amyrin                                                | Invitro | *T.b.r*     | >90, 38.6 and >90 μg/ml         | 15.56, 15.78, 11.21 μg/ml | Kenya     | (Mwangi et al., 2010)       |
| *Terminalia actinophylla* Mart. | Combretaceae     | Leaf         | Water      | Terchebulin and punicalagin                                                           | Invitro | *T.b.b*     | ≥1500 and ≥1500 μg/ml          | 25 and 14 μM | Nigeria   | (Shuaib et al., 2008)       |
| *Toona ciliata* M.Roem.         | Meliaceae        | Root         | Methanol   | Cedrelone                                                                             | Invitro | *T.b.r*     | -                               | 6.95\(^{Me}\) 3.2\(^{Cr}\) and 7.85 | Kenya     | (Githua and Hassanali, 2011)|
| *Vernonia guineensis* Benth.    | Asteraceae       | Stem bark    | Ethanol    | Vernoguinosterol and vernoguninoside                                                  | Invitro | *T.b.r*     | -                               | 3–5 μg/ml | Cameroon  | (Tchinda et al., 2002)      |
| *Vernonia mespilifolia* Less.   | Asteraceae       | Leaf         | DCM/methanol | Cynaropicrin                                                                        | Invitro | *T.b.r/T.cr*| 1.29 μM                       | 0.23 μM/5.14 μM | South Africa | (Mokoka et al., 2013)    |
| *Waltheria indica* L.           | Malvaceae        | Root         | DCM        | Waltheriones L                                                                       | Invitro | *T.cr/T.bb/T.b.r* | -                     | 0.74\(^{C}20\)^, 17.4 (μg/ml) and 3.1 μM | Cameroon  | (Simoben et al., 2018)      |
| *Warburgia ugandensis* subsp. ugandensis | Canellaceae | Leaf        | DCM        | Muzigadiolide, muzigadial, 6α,9α-dihydroxy-4(13),7-dihydroxy-11,12-dial and mukaadial and ugandensidal | Invitro | *T.b.r* | -                               | 0.64 to 6.4 μM | Cameroon  | (Simoben et al., 2018)      |
| *Zapoteca portoricensis* (Jacq.) H.M.Hem. | Fabaceae          | Leaf       | DCM        | Saropeptide or aurantiamide acetate                                                  | Invitro | *T.b.r/T.c* | 92.05 μM                        | 3.63 and 41.65 μM | Cameroon  | (Simoben et al., 2018)      |

Abbreviations: EC50, half maximal inhibitory concentration (μg/ml); T.b. b, Trypanosoma brucei brucei; T.e, Trypanosoma evansi; T. co, Trypanosoma congolense; \( ^{Me} \) Me: Methanolic extract; \( ^{Cr} \) Ce: Chloroform extract.
anti-trypanosomal medicine based on plants has been an exciting research topic.

Additionally, the medicinal plants of Africa provide a large variety of bioactive compounds. Of the 24 plants reported in Table 1, approximately 34 different bioactive compounds were isolated with trypanosomiasis activity. Some plants, such as *Chrysanthemum cinerariifolium*, *Keetia leucantha*, *Tecla trichocarpa* and *Terminalia avicenoides*, provide at least three different potent bioactive compounds. Concerning the criteria for choosing compounds with anti-trypanosomal potential, EC50 > 20 μg/ml is considered ineffective (Pink et al., 2005). Thus, approximately 40 compounds seem to be effective (EC50 < 20 μg/ml) and have demonstrated promising anti-trypanocidal activity (Figure 2). Given the minimum inhibitory concentration, only abruquinone (0.01 μg/ml) has a concentration closer to Melarsoprol reference (0.004 μg/ml) was active against *Trypanosoma brucei* and benznidazole (0.482 μg/ml) reference was active against *Trypanosoma cruzi*.

### 3.3 Asia plants

Asia plants assessed for anti-trypanosomal activity with EC50 values for inhibition of parasites and cytotoxicity are shown in Table 2.

A total of 31 plants with their minimum inhibitory concentration have been identified in the literature. Four plants (*V. repens*, *P. simplex*, *V. arborea* and *A. brevipedunculata*) already have bioactive compounds. These seven compounds include resveratrol (EC50 = 31.4), 11-O-acetyl-bergenin (EC50 = 61.2), stigmas-4-en-3-one (EC50 = 62.8), lupeol (EC50 = 98.4), Ψ-taraxasterone (EC50 = 115.4), hopenyl-3β-O-palmitate (EC50 = 68.2) and β-amyrin palmitate (EC50 = 60.8) (Bawm, 2010). The extracts were mostly evaluated on *Trypanosoma evansi* due to its prevalence in Asia (Dyary et al., 2014). Considering the potency criteria asserted by Pink et al. (2005), it was expressed that the isolated compounds with an EC50 > 20 μg/ml were not considered effective drugs. Thus, the seven isolated compounds may not be considered lead drugs. There is a need to pursue investigations that isolate more...
FIGURE 2  Chemical structures of isolated compounds from Africa medicinal plants
FIGURE 2 Continued
FIGURE 2 Continued

FIGURE 3 Chemical structures of isolated compounds from Asia medicinal plants
**Table 2**  Plants assessed for anti-trypanosomal activity in *in vitro* model

| Scientific name       | Family             | Part(s) used | Solvent     | Bioactive compound          | Sub species | EC50       | CC50*   | Country | References            |
|-----------------------|--------------------|--------------|-------------|-----------------------------|-------------|------------|---------|---------|-----------------------|
| *Alnus japonica*      | Betulaceae         | Bark         | DCM         | Oregonin                    | Tb          | 1.14 and 1.78 μM | 50 μM   | Japan   | (Tung et al., 2014)   |
| *Aquilaria malaccensis* | Thymelaeaceae     | Leaves       | Ethanol     | -                            | Te          | 128.63 μg/ml     | 259.78 μg/ml | Malaysia | (Dyary et al., 2014) |
| *Andrographis paniculata* | Acanthaceae     | Leaves/stems | Methanol    | -                            | Te          | 54.7 μg/ml       | 55.1 μg/ml | Japan   | (Bawm, 2010)           |
| *Brucea javanica*     | Simaroubaceae      | Fruit        | Methanol    | -                            | Te          | 27.2 μg/ml       | 309.15 μg/ml | Japan   | (Bawm, 2010)           |
| *Combretum acuminatum* | Combretaceae      | Rhizomes     | Methanol    | -                            | Te          | 90.7 μg/ml       | 853.15 μg/ml | Japan   | (Bawm, 2010)           |
| *Cordyline terminalis* | Liliaceae         | Leaves       | Water       | -                            | Te          | 48.1 μg/ml       | -       | Malaysia | (Dyary et al., 2019)   |
| *Crataeva religiosa*  | Capparidaceae      | Leaves/stems | Methanol    | -                            | Te          | 107.1 μg/ml      | 691 μg/ml    | Japan   | (Bawm, 2010)           |
| *Curcuma longa*       | Zingiberaceae      | Leaves       | Oil         | Curlone                     | T.b.b       | 1.38 μg/ml       | -       | Vietnam | (Le et al., 2019)      |
| *Curcuma zedoaria*    | Zingiberaceae      | Leaves       | Oil         | -                            | T.b.b       | 2.51 μg/ml       | -       | Vietnam | (Le et al., 2019)      |
| *Derris elliptica*    | Fabaceae           | Leaves       | Ethanolic   | -                            | Te          | 17.79 μg/ml      | 331.90 μg/ml | Malaysia | (Dyary et al., 2014)   |
| *Eucalyptus globulus* | Myrtaceae          | Leaf         | Methanol    | -                            | Te          | 51.1 μg/ml       | 622.95 μg/ml | Japan   | (Bawm, 2010)           |
| *Garcinia hombroniana* | Clusiaceae         | Leaves       | Ethanolic   | -                            | Te          | 103.44 μg/ml     | 10.17 μg/ml  | Malaysia | (Dyary et al., 2014)   |
| *Goniolthalamus tapis* | Annonaceae         | Leaves       | Ethanolic   | -                            | Te          | 7.61 μg/ml       | -       | Malaysia | (Dyary et al., 2019)   |
| *Goniolthalamus umbrosus* | Annonaceae | Leaves       | Ethanolic   | -                            | Te          | 2.30 μg/ml       | 29.10 μg/ml  | Malaysia | (Dyary et al., 2014)   |
| *Iris domestica*      | Iridaceae          | Leaves       | Petroleum ether | Isosirodigermanal      | T.b.b       | 3.60 μg/ml       | 136.00 μg/ml | China   | (Pathiranage et al., 2016) |
| *Jatropha podagrica*  | Euphorbiaceae      | Fruit        | Methanol    | -                            | Te          | 52.3 μg/ml       | 652.7 μg/ml  | Japan   | (Bawm, 2010)           |
| *Litsea cubeba*       | Lauraceae          | Leaves       | Oil         | -                            | T.b.b       | 1.12 nL/ml       | -       | Vietnam | (Le et al., 2019)      |
| *Murraya koenigii*    | Rutaceae           | Leaves       | Mahanimbine, murrayafoline and girinimbine | T.e          | 3.13, 6.35 and 10.16 μg/ml | 745.58 μg/ml | 10.16 μg/ml | Malaysia | (Dyary et al., 2019)   |
| *Nigella sativa*      | Ranunculaceae      | Seeds        | Ethanolic   | -                            | Te          | 291.72 μg/ml     | 381.59 μg/ml | Malaysia | (Dyary et al., 2014)   |

(Continues)
| Scientific name           | Family            | Part(s) used | Solvent | Bioactive compound | Sub species | EC50*  | CC50* | Country  | References          |
|---------------------------|-------------------|--------------|---------|--------------------|-------------|--------|-------|-----------|----------------------|
| Orthosiphon stamineus    | Labiatae          | Leaves       | Methanol| -                  | Te          | 144.7μg/ml | 628.9μg/ml | Japan     | (Bawm, 2010)         |
| Phyllanthus simplex Retz. | Euphorbiaceae     | Leaves/ stem | Methanol| -                  | Te          | 96.1μg/ml  | 98.8μg/ml | Japan     | (Bawm, 2010)         |
| Plumbago rosea L.        | Plumbaginaceae    | Flowers      | Methanol| -                  | Te          | 156.7μg/ml | 557.05μg/ml| Japan     | (Bawm, 2010)         |
| Polygonum hydropiper L.  | Polygonaceae      | Leaves       | DCM     | Vanicoside E, (+)-ketopinoresinol, isorhamnetin and cardamom | Tb          | 0.49–7.77μg/ml | -      | China     | (Xiao et al., 2017) |
| Punica granatum L.       | Lythraceae        | Leaves       | Ethanol | -                  | Te          | 20 mg/ml   | -      | India     | (Kumar et al., 2014) |
| Quercus borealis F.Michx.| Fagaceae          | Roots        | Methanol| -                  | Te          | 250 μg/ml  | -      | India     | (Shaba et al., 2011) |
| Rhoeo discolor L'Hér. Hance | Commelinaceae     | Leaves       | Methanol| -                  | Te          | 75.8 μg/ml | 424.9 μg/ml| Japan     | (Bawm, 2010)         |
| Scutellaria baicalensis Georgi | Lamium & Ch | Leaves       | Water/ chloroform | -                  | Tb          | 11.43 μg/ml | 19.56 μg/ml| China     | (Floyd, 2013)        |
| Strobilanthes abbreviata Y.F. Deng & J.R.I. Wood | Acanthaceae | Leaves       | Ethanolic| -                  | Te          | 52.54 μg/ml | 355.21 μg/ml| Malaysia  | (Dyary et al., 2014) |
| Vitex arborea Desf.      | Verbenaceae       | Leaves/ stem | Methanol| -                  | Te          | 48.6 μg/ml | 735.15 μg/ml| Japan     | (Bawm, 2010)         |
| Vitis repens Lam. Wight & Arn. | Vitaceae         | Root bark    | Methanol| -                  | Te          | 8.6 μg/ml  | 209.9 μg/ml| Japan     | (Bawm, 2010)         |
| Zingiber officinal Roscoe | Zingiberaceae     | Leaves       | Oil     | -                  | Tb.b        | 3.10 nL/ml | -      | Vietnam   | (Le et al., 2019)    |

Note: The EC50 values for inhibition of parasites and the cytotoxicity are shown
*The extract concentration that reduced the cell viability by 50% when compared to untreated controls.

effective compounds. On the other hand, as suggested by Pink et al. (2005), crude extracts with potent in vivo anti-trypanosomal activity such as <100 mg/kg with no toxic effect below 800 mg/kg may be considered promising lead structures. None of the plants with in vitro data were evaluated in vivo. The minimum inhibitory concentration of the methanolic extract of Goniothalamus umbrosus (2.30 μg/ml) was the only extract with an activity profile closer to the diminazene acetate (0.01140 μg/ml) reference against Trypanosoma evansi.

3.4 | Middle East

Table 3 shows a list of plants in the Middle East with cytotoxicity values against trypanosome parasite activity. Al-Musayeib et al. (2012) reported 41 medicinal plants used in Saudi Arabia that showed anti-trypanosomal activity in vitro. All of their inhibitory activities are explained by the EC50 and CC50. However, no details have been given about their bioactive compounds except their secondary metabolite composition. Their activity profile in in vivo studies is unknown, so their therapeutic potential remains to be established.

3.5 | European plants

A total of 27 plants studied in Europe have been extracted from the literature. Of these, only three plants have bioactive compounds. The milestone was the most efficient bioactive compound with a minimum inhibitory concentration of 0.5 μg/ml (Ślusarczyk et al., 2011). Trypanosoma brucei was the most studied parasite, and a large variety of ethnobotanical families were included (Table 4 and Figure 4).
| Scientific Name | Family | Part(s) used | Solvent | Sub species | EC50 | CC50 | References |
|----------------|--------|-------------|---------|-------------|------|------|------------|
| Ajuga bracteosa | Labiatae | Leaves | Methanol | T.c T.b.b | 28.8 μg/ml 31.2 μg/ml | (Al-Musayeib, Mothana, Matheeussen, et al., 2012) |
| Albizia lebbeck (L.) Benth. | Leguminosae | Stems | Methanol | T.c T.b.b | 8.7 μg/ml 8.1 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Cadaba farinosa subsp. adenotricha (Gilg & Benedict) R.A.Graham | Capparaceae | Leaves/stems | Methanol | T.c T.b.b | 28.6 μg/ml 10.6 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Cadaba glandulosa Forssk. | Capparaceae | Leaves/stems | Methanol | T.c T.b.b | >64.0 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Caralluma quadrangula (Forssk.) N.E.Br. | Asclepiadaceae | Leaves | Methanol | T.c T.b.b | >64.0 μg/ml 32.5 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Caralluma sinaica (Decne.) A.Berger | Asclepiadaceae | Leaves | Methanol | T.c T.b.b | 7.3 μg/ml 7.7 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Celtis africana Burm.f. | Cannabaceae | Leaves/stems | Methanol | T.c T.b.b | >64.0 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Centaurea pseudosinica Czerep. | Asteraceae | Leaves | Methanol | T.c T.b.b | 31.0 μg/ml 9.1 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Chrozophora oblongifolia (Delile) A.Juss. ex Spreng. | Euphorbiaceae | Leaves | Methanol | T.c T.b.b | 32.0 μg/ml 10.8 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Conocarpus lancifolius Engl. | Combretaceae | Fruits | Methanol | T.c T.b.b | 32.2 μg/ml 35.2 μg/ml | 7.2 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Cordia sinensis Lam. | Boragineae | Leaves/stems | Methanol | T.c T.b.b | 33.9 μg/ml 32.0 μg/ml | >64.0 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Costus arabicus L. | Zingiberaceae | Roots | Methanol | T.c T.b.b | 13.8 μg/ml 30.0 μg/ml | 38.5 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Cupressus sempervirens L. | Cupressaceae | Leaves | Methanol | T.c T.b.b | 8.3 μg/ml 2.1 μg/ml | 10.7 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Dorstenia barnimiana Schweinf. | Moraceae | Leaves | Methanol | T.c T.b.b | 29.6 μg/ml 22.6 μg/ml | 49.4 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Dodonaea viscosa (L.) Jacq. | Sapindaceae | Leaves | Methanol | T.c T.b.b | >64.0 μg/ml 11.1 μg/ml | >64.0 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Enicostemma verticillare L. | Gentianaceae | Leaves | Methanol | T.c T.b.b | >64.0 μg/ml | 9.9 ± 1.1 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Ficus cordata subsp. salicifolia (Vahl) C.C.Berg | Moraceae | Leaves | Methanol | T.c T.b.b | 26.3 μg/ml 8.2 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Scientific Name                      | Family                  | Part(s) Used | Solvent  | Subspecies | EC50      | CC50      | References                                                                 |
|-------------------------------------|-------------------------|--------------|----------|------------|-----------|-----------|-----------------------------------------------------------------------------|
| Ficus ingens (Miq.) Miq.            | Moraceae                | Leaves       | Methanol | T.c        | 31.2 μg/ml| 32.5 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      |           |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Ficus palmata                        | Moraceae                | Leaves       | Methanol | T.c        | 22.6 μg/ml| 37.7 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
| subsp. virgata Browicz              |                         |              |          | T.b.b      |           |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Grewia erythraea                     | Tiliaceae               | Leaves       | Methanol | T.c        | 8.2 μg/ml | 27.2 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
| Schweinit.                          |                         |              |          | T.b.b      |           |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Iris albiacns var. madonna Dykes     | Iridaceae               | Leaves       | Methanol | T.c        | >64.0 μg/ml| >64.0 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 10.6 μg/ml|           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Iris germanica L.                   | Iridaceae               | Roots        | Methanol | T.c        | 24.6 μg/ml| >64.0 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 8.2 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Kanaha laniflora (Forssk.) R.Br.    | Iridaceae               | Leaves       | Methanol | T.c        | 0.4 μg/ml | 0.8 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 9.6 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Kniphofia sumarae Deflers            | Asclepiadaceae         | Leaves       | Methanol | T.c        | 31.4 μg/ml| 7.4 μg/ml | (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 5.9 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Lavandula dentata var. candicans Batt. | Liliaceae             | Leaves       | Methanol | T.c        | 7.9 μg/ml | 29.6 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 3.0 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Leucas inflata Benth.               | Labiatae               | Leaves       | Methanol | T.c        | >64.0 μg/ml| 29.5 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 8.4 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Nigella sativa var. hispidula Boiss. | Ranunculaceae         | Seeds        | Methanol | T.c        | >64.0 μg/ml| >64.0 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | >64.0 μg/ml|           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Periploca aphylla Decne.            | Asclepiadaceae         | Leaves/stems | Methanol | T.c        | 8.1 μg/ml | 23.9 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 7.1 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Phoenix dactylifera L.              | Areaceae               | Seeds        | Methanol | T.c        | 46.5 μg/ml| >64.0 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 36.2 μg/ml|           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Plectranthus barbatus var. grandis  | Labiatae               | Leaves       | Methanol | T.c        | 23.3 μg/ml| 32.9 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
| (L.H.Cramer) Lukhoba & A.J.Paton    |                         |              |          | T.b.b      | 2.6 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Prosopis juliflora var. horrida     | Leguminosae            | Fruits       | Methanol | T.c        | 10.4 μg/ml| 49.8 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
| (Kunth) Burkart                     |                         |              |          | T.b.b      | 2.0 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Pulicaria inuloides (Poir.) DC.     | Labiatae               | Leaves       | Methanol | T.c        | 31.7 μg/ml| >64.0 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 7.8 μg/ml |           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Punica granatum L.                  | Punicaceae             | Fruits       | Methanol | T.c        | 35.2 μg/ml| >64.0 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 34.3 μg/ml|           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |
| Rhus retinorrhoea Steud. ex A.Rich. | Anacardiaceae         | Leaves       | Methanol | T.c        | 30.5 μg/ml| 53.2 μg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012)                          |
|                                     |                         |              |          | T.b.b      | 34.0 μg/ml|           |                                                                             |
|                                     |                         |              |          |            |           |           |                                                                             |

(Continues)
### TABLE 3 (Continued)

| Scientific Name                  | Family               | Part(s) used | Solvent | Subspecies | EC50       | CC50       | References                                      |
|----------------------------------|----------------------|--------------|---------|------------|------------|-----------|------------------------------------------------|
| *Ribes nigrum* L.                | Grossulariaceae      | Fruits       | Methanol| T. c       | >64.0 µg/ml| >64.0 µg/ml| (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| *Salvadora persica* var. persica | Salvadoraaceae       | Leaves/stems | Methanol| T. c       | 30.1 µg/ml | 32.0 µg/ml| >64.0 µg/ml (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| *Tagetes minuta* L.              | Asteraceae           | Leaves       | Methanol| T. c       | 9.2 µg/ml  | 2.2 µg/ml  | >64.0 µg/ml (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| *Tarconanthus camphoratus* L.    | Asteraceae           | Leaves       | Methanol| T. c       | >64.0 µg/ml| >64.0 µg/ml| >64.0 µg/ml (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| *Teucrium yemense* Deflers       | Labiatae             | Leaves       | Methanol| T. c       | 30.5 µg/ml | 7.1 µg/ml  | 27.2 µg/ml (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| *Vernonia leopoldi* (Sch.Bip. ex  | Asteraceae           | Leaves       | Methanol| T. c       | 9.2 µg/ml  | 8.0 µg/ml  | 30.1 µg/ml (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| Walp.) Vatke                     |                      |              |         | T. b.b     |            |           |                                                |
| *Zingiber officinale* var.      | Zingiberaceae        | Roots        | Methanol| T. c       | >64.0 µg/ml| 39.4 µg/ml| 34.3 µg/ml (Al-Musayeib, Mothana, Al-Massarani, et al., 2012) |
| *cholmondeleyi* F.M.Bailey       |                      |              |         | T. b.b     |            |           |                                                |

![FIGURE 4](image4.png)

**Chemical structures of isolated compounds from Europe medicinal plants**

### 3.6 Latin America

A total of 165 plants have been reported throughout the literature, and just four have their isolated known compound. Researchers from South America have contributed to the investigation of anti-trypanosomal plants. This result corroborates the scientometric analysis of global trypanosomiasis research from 1988 to 2017, showing that South America ranked second behind Europe for contributions to trypanosomiasis research (Hassan et al., 2020). The crude extracts of *Anthemis tinctoria* (semi-purified), *Caseria sylvestris* (hexane) and *Ranunculus sceleratus* (ethanol) showed inhibitory activity against *Trypanosoma cruzi* with a minimum inhibitory concentration of 0.2, 0.3 and 0.7 µg/ml, respectively. For many plants, parasite growth inhibition is generally reported; thus, the minimum inhibitory concentration remains unknown (Table 5 and Figure 5).

![FIGURE 5](image5.png)

**Chemical structures of isolated compounds from Latin America medicinal plants**
| Scientific name                      | Family           | Part(s) used | Solvent | Bioactive compound | Model | Subspecies | EC50     | CC50    | Country      | References                          |
|-------------------------------------|------------------|--------------|---------|-------------------|-------|------------|----------|--------|--------------|-------------------------------------|
| Arctium nemorosum Lej.              | Asteraceae       | Leaf         | Methanol| Onopordopicrin    | In vitro | T.b.r      | 0.37 μM  | 3.06 μM | Switzerland  | (Zimmermann et al., 2012)           |
| Arnica montana L.                   | Asteraceae       | Leaf         | DCM     | -                 | In vitro | T.b.r      | 1.12 μg/ml | 12.1 μg/ml | Germany      | (Llurba-Montesino et al., 2015)     |
| Callitris neocaledonica Dümmer      | Cupressaceae     | Wood         | Water   | -                 | In vitro | T.b.b      | >50 μg/ml | >50 μg/ml | France       | (Desrivot et al., 2007)             |
| Callitris sulcata (Parl.) Schltr.   | Cupressaceae     | Wood         | Water   | -                 | In vitro | T.b.b      | >50 μg/ml | >50 μg/ml | France       | (Desrivot et al., 2007)             |
| Citrus macroptera Montrouz.         | Rutaceae         | Leaves       | Water   | -                 | In vitro | T.b.b      | >50 μg/ml | >50 μg/ml | France       | (Desrivot et al., 2007)             |
| Crinum stuhlmannii subsp. delagoense (L. Verd.) Kwembeya & Nordal | Amaryllidaceae | Leaves       | Ethanol | -                 | In vitro | T.c       | 0.70 μM  | 21.87 μM | Spain        | (Martinez-Peinado et al., 2020)     |
| Curcuma longa L.                    | Zingiberaceae    | Leaves       | Water   | -                 | In vitro | T.b.b      | >50 μg/ml | -        | France       | (Desrivot et al., 2007)             |
| Dodonea viscosa L.                  | Sapindaceae      | Leaves       | Ethanol | -                 | In vitro | T.b.b      | 61.4 μg/ml | -        | France       | (Desrivot et al., 2007)             |
| Eugenia uniflora L.                 | Myrtaceae        | Bark         | Water   | -                 | In vitro | T.b.b      | >50 μg/ml | -        | France       | (Desrivot et al., 2007)             |
| Eugenia uniflora L.                 | Moraceae         | Leaves       | Methanol| -                 | In vitro | T.b.b      | 46 μg/ml  | -        | France       | (Desrivot et al., 2007)             |
| Hernandia cordigera Viei.           | Hernandiaceae    | Bark         | DCM     | -                 | In vitro | T.b.b      | 48 μg/ml  | -        | France       | (Desrivot et al., 2007)             |
| Homalium deplanchei Warb.           | Flacourtiaceae   | Bark         | DCM     | -                 | In vitro | T.b.b      | >50 μg/ml | -        | France       | (Desrivot et al., 2007)             |
| Hyacinthoides non-scripta (L.) Chauard ex Rothm. | Asparagaceae     | Flowers      | Methanol| -                 | In vitro | T.b.b      | 11.1 μg/ml | -        | UK           | (Raheem et al., 2019)               |
| Juncus acutus subsp. acutus         | Juncaceae        | Leaves       | DCM     | Juncunol          | In vitro | T.c       | 4.1 μg/ml | 6.0 μg/ml | Portugal     | (Oliveira et al., 2016)             |
| Manilkara dissecta (L.f.) Dubard    | Sapotaceae       | Leaves       | DCM     | -                 | In vitro | T.b.b      | >50 μg/ml | -        | France       | (Desrivot et al., 2007)             |

(Continues)
| Scientific name                        | Family                | Part(s) used | Solvent | Bioactive compound | Model | Subspecies | EC50  | CC50 | Country | References                      |
|----------------------------------------|-----------------------|--------------|---------|--------------------|-------|------------|-------|------|---------|----------------------------------|
| *Murraya crenulata* (Turcz.) Oliv.     | Rutaceae              | Bark         | Hexane  | -                  | In vitro | Tb.b       | 27.6 μg/ml | -    | France  | (Desrivat et al., 2007)          |
| *Myoporum crassifolium* G.Forst.       | Myoporaceae           | Wood         | Water   | -                  | In vitro | Tb.b       | 16 μg/ml   | -    | France  | (Desrivat et al., 2007)          |
| *Myoporum tenuifolium* G.Forst.        | Myoporaceae           | Leaves       | DCM     | -                  | In vitro | Tb.b       | >50 μg/ml  | -    | France  | (Desrivat et al., 2007)          |
| *Myristica fatua* Houtt.               | Myristicaceae         | Almonds      | DCM     | -                  | In vitro | Tb.b       | 0.5 μg/ml  | -    | France  | (Desrivat et al., 2007)          |
| *Narcissus broussonetii var.*          | Amaryllidaceae        | Leaves       | Ethanol | -                  | In vitro | Tc         | 0.495 μM  | 5.21 μM | Espain  | (Martinez-Peinado et al., 2020) |
| *Myristica fatua* Houtt.               | Myristicaceae         | Almonds      | DCM     | -                  | In vitro | Tb.b       | >50 μg/ml  | -    | France  | (Desrivat et al., 2007)          |
| *Narcissus broussonetii var.*          | Amaryllidaceae        | Leaves       | Ethanol | -                  | In vitro | Tb.b       | >50 μg/ml  | -    | France  | (Desrivat et al., 2007)          |
| *Prema serratifolia* L.                | Lamiaceae             | Bark         | DCM     | -                  | In vitro | Tb.b       | >50 μg/ml  | -    | France  | (Desrivat et al., 2007)          |
| *Prumnopitys ferruginoides* L.         | Podocarpaceae         | Leaves       | Water   | -                  | In vitro | Tb.b       | >50 μg/ml  | -    | France  | (Desrivat et al., 2007)          |
| *Salvia officinalis subsp.*            | Lamiaceae             | Leaves       | DCM     | -                  | In vitro | Tb.r       | 1.86 μg/ml | 32.3 μg/ml | Switzerland | (Llurba-Montesinos et al., 2015) |
| *Salvia miltiorrhiza* var.*            | Lamiaceae             | Roots        | DCM     | Miltirone          | In vitro | Tb.r       | 0.5 μg/ml  | 1.3 μg/ml | Switzerland | (Skurszyczyk et al., 2011)       |
| *Salvia miltiorrhiza* var.*            | Lamiaceae             | Roots        | DCM     | Miltirone          | In vitro | Tb.r       | 0.5 μg/ml  | 1.3 μg/ml | Switzerland | (Skurszyczyk et al., 2011)       |
| *Scaevola balansae* Guillouin          | Goodeniaceae          | Bark         | DCM     | -                  | In vitro | Tb.b       | 39 μg/ml   | -    | France  | (Desrivat et al., 2007)          |
| *Valeriana officinalis subsp.*         | Caprifoliaceae        | Leaves       | Ethanol | -                  | In vitro | Tc         | 5.87 μg/ml | 5.28 μg/ml | Germany  | (Llurba-Montesinos et al., 2015) |
| *Wallstania biflora* (L.) DC.          | Asteraceae            | Leaves       | DCM     | -                  | In vitro | Tb.b       | >100 μg/ml | -    | France  | (Desrivat et al., 2007)          |
| Scientific name | Family | Part(s) used | Solvent | Bioactive compound | Model | Sub species | EC50 | CC50 | Country | References |
|-----------------|--------|--------------|---------|--------------------|-------|-------------|------|------|---------|------------|
| *Abuta pahni* (Mart.) Krukoff & Barneby | Menispermaceae | Stems | Petroleum ether, chloroform, ethyl acetate or 50% ethanol | - | In vitro | T.c | 100 μg/ml | - | Bolivia | (Fournet et al., 1994) |
| *Acnistus arborescens* (L.) Schltdl. | Solanaceae | Leaf | Ethanol | - | In vitro | T.c | 4 μg/ml | - | Panama | (Calderón et al., 2010) |
| *Aechmea distichantha var. glaziouii* (Baker) L.B.Sm. | Bromeliaceae | Leaf | Methanol | - | In vitro | T.c | 48 μg/ml | - | Panama | (Calderón et al., 2010) |
| *Aloe trigonophylla* Meissn. | Lauraceae | Leaf | Ethanol | *Sesquiterpene Lactone* A | In vitro | T.c | 2.75 μg/ml | 156.45 μg/ml | Brazil | (Nunes et al., 2020) |
| *Angelica dahurica* (Hoffm.) Berth. & Hook.f. ex Franch. & Sav. | Apiaceae | Root | Ethanol | - | In vitro | T.c | 14.5 μg/ml | - | Argentina | (Schinella et al., 2002) |
| *Angelica pubescens f. biserrata* R.H.Shan & C.Q.Yuan | Apiaceae | Root | Ethanol | - | In vitro | T.c | 14.9 μg/ml | - | Argentina | (Schinella et al., 2002) |
| *Angelica sinensis* (Oliv.) Diels | Apiaceae | Wood | Ethanol | - | In vitro | T.c | 19.4 μg/ml | - | Argentina | (Schinella et al., 2002) |
| *Annona crassiflora* Mart. | Annonaceae | Root bark | Ethanol | - | In vitro | T.c | 5.9 μg/ml | - | Brazil | (Mesquita et al., 2005) |
| *Annona muricata* L. | Annonaceae | Leaf | Ethanol | - | In vitro | T.c | 10 μg/ml | - | Panama | (Calderón et al., 2010) |
| *Anomospermum chloranthum* subsp. occidentale (Cuatrec.) Krukoff & Barneby | Menispermaceae | Leaf | Alkaloid | - | In vitro | T.c | 100 μg/ml | - | Bolivia | (Fournet et al., 1994) |
| *Anthemis tinctoria* subsp. australis R.Fern. | Asteraceae | Flowers | Semi-purified | - | In vitro | T.c | 0.2 μg/ml | 7.0 μg/ml | Brazil | (Bittencourt et al., 2011) |
| *Astragalus pehuencenis* Niederl. | Fabaceae | Bark | Methanol | - | In vitro | T.c | > 50 μg/ml | - | Panama | (Calderón et al., 2010) |
| *Ardisia densiflora* Krug & Urb. | Myrsinaceae | Leaf | Ethanol | - | In vitro | T.c | > 50 μg/ml | - | Panama | (Calderón et al., 2010) |
| *Argemone subfusiformis* Ownbey | Papaveraceae | Fruit | Methanol | - | In vitro | T.c | 10 μg/ml | - | Panama | (Calderón et al., 2010) |
| Scientific name                      | Family               | Part(s) used | Solvent | Bioactive compound | Model | Sub species | EC50     | CC50     | Country | References                  |
|--------------------------------------|----------------------|--------------|---------|--------------------|-------|-------------|----------|----------|---------|------------------------------|
| *Aristolochia pilosa* L.             | Aristolochiaceae     | Stem         | Hexane  | -                  | In vitro | T.c         | 100%     | -        | Peru    | (González-Coloma et al., 2012) |
| *Artemisia mexicana* Willd.          | Asteraceae           | Aerial parts | Methanol| -                  | In vitro | T.c         | 39.25 μg/ml | -        | Mexico  | (Molina-Garza et al., 2014)   |
| *Atractylodes macrocephala* L.      | Asteraceae           | Root         | Ethanol | -                  | In vitro | T.c         | 23.0 μg/ml | -        | Argentina | (Schnella et al., 2002)       |
| *Astragalus membranaceus* (Fisch.) Bunge | Fabaceae            | Root         | Water   | -                  | In vitro | T.c         | 13.5 μg/ml | -        | Argentina | (Schnella et al., 2002)       |
| *Astronium fraxinifolium* Schott     | Anacardiaceae        | Stems bark   | Hexane  | -                  | In vitro | T.b.r       | 16.4 μg/ml | >100 μg/ml | Brazil  | (Charneau et al., 2016)       |
| *Baccharis notosergila* Griseb.      | Asteraceae           | Aerial parts | Methanol| -                  | In vitro | T.c         | >50 μg/ml | -        | Panama  | (Calderón et al., 2010)       |
| *Baccharis trinervis var. cinerea* (DC.) Baker | Asteraceae          | Aerial parts | Ethanol | -                  | In vitro | T.c         | >50 μg/ml | -        | Panama  | (Calderón et al., 2010)       |
| *Berberis conferta var. boliviana* (Lechtl.) C.K.Schneid. | Berberidaceae       | Stems        | Alkaloid | -                  | In vitro | T.c         | 75 μg/ml  | -        | Bolivia | (Fournet et al., 1994)        |
| *Berberis microphylla* G.Forst.      | Berberidaceae        | Aerial parts | Methanol| -                  | In vitro | T.c         | 38.4 μg/ml | -        | Chile   | (Muñoz et al., 2013)          |
| *Blepharocalyx salicifolius* (Kunth) O.Berg | Myrtaceae           | Leaves       | Ethanol | -                  | In vitro | T.c         | 37.3 μg/ml | 55.1 μg/ml | Brazil  | (Charneau et al., 2016)       |
| *Bocconia integrifolia var. mexicana* DC. | Papaveraceae        | Leaf         | Ethanol | -                  | In vitro | T.c         | >50 μg/ml | -        | Panama  | (Calderón et al., 2010)       |
| *Bourreria huanita* (Lex.) Hemel.    | Boraginaceae         | Leaf         | Ethanol | -                  | In vitro | T.c         | >50 μg/ml | -        | Panama  | (Calderón et al., 2010)       |
| *Bourreria spathulata* (Miers) Hemsl. | Boraginaceae         | Leaf         | Methanol| -                  | In vitro | T.c         | 30 μg/ml  | -        | Panama  | (Calderón et al., 2010)       |
| *Brunfelsia grandiflora* D.Don       | Solanaceae           | Stem         | Hexane  | -                  | In vitro | T.c         | 98%      | -        | Peru    | (González-Coloma et al., 2012) |
| *Caesalpinia paraguariensis* (Parodi) Burkart | Fabaceae            | Leaf         | Ethanol | -                  | In vitro | T.c         | 10 μg/ml  | -        | Panama  | (Calderón et al., 2010)       |
| *Calea jamaicensis* var. jamaicensis | Asteraceae           | Aerial parts | Ethanol | -                  | In vitro | T.c         | 30 μg/ml  | -        | Panama  | (Calderón et al., 2010)       |

(Continues)
| Scientific name | Family | Part(s) used | Solvent | Bioactive compound | Model | Sub species | EC50 | CC50 | Country | References |
|-----------------|--------|--------------|---------|--------------------|-------|-------------|------|------|---------|------------|
| *Calea peruviana* (Kunth) Benth. ex S.F.Blake | Asteraceae | Leaf | Ethanol | - | In vitro | *T.c* | > 50 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Capraira biflora* f. *hirta* Loes. | Scrophulariaceae | Aerial parts | Ethanol | - | In vitro | *T.c* | 46 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Capparis salicifolia* Griseb. | Capparaceae | Leaf | Ethanol | - | In vitro | *T.c* | 39 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Cardiopetalum calophyllum* Schltdl. | Annonaceae | Stem bark | Hexane | - | In vitro | *T.c* | 60.4 µg/ml | - | Brazil | (Mesquita et al., 2005) |
| *Cardiopetalum calophyllum* Schltdl. | Annonaceae | Leaves | Alkaloidal | - | In vitro | *T.c* | 100 µg/ml | - | Bolivia | (Fournet et al, 1994) |
| *Casearia sylvestris* var. *lingua* (Cambess.) Eichler | Flacourtiaceae | Root bark | Hexane | - | In vitro | *T.c* | 0.3 µg/ml | - | Brazil | (Mesquita et al., 2005) |
| *Cedrela odorata* var. *xerogetona* Rizzini & Heringer | Meliaceae | Bark | Hexane | - | In vitro | *T.c* | 100% | - | Peru | (González-Coloma et al., 2012) |
| *Cestrum parqui* (Lam.) L’Hér. | Solanaceae | Aerial parts | Ethanol | - | In vitro | *T.c* | > 50 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Chamaecrista desvauxii* (Collad.) Killip | Caesalpiniaceae | Leaves | Ethanol | - | In vitro | *T.c* | >80% | - | Brazil | (Charneau et al., 2016) |
| *Chondodendron tomentosum* L. | Menispermaceae | Bark | Chloroform | - | In vitro | *T.c* | 100% | - | Peru | (González-Coloma et al., 2012) |
| *Chromolaena leivensis* (Hieron.) R.M.King & H.Rob. | Asteraceae | Aerial parts | Ethanol | - | In vitro | *T.c* | 8 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Cinchona pubescens* var. *heterophylla* Pav ex DC. | Rubiaceae | Leaf | Methanol | - | In vitro | *T.c* | > 50 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Cissampelos tropaeolifolia* var. *fluminensis* (Eichler) Diels | Menispermaceae | Leaf | Ethanol | - | In vitro | *T.c* | >50 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Clarisia biflora* Ruiz & Pav. | Moraceae | Aerial parts | Ethanol | - | In vitro | *T.c* | 25 µg/ml | - | Panama | (Calderón et al., 2010) |
| *Clematis commepstris* var. *mendocina* (Phil.) Hauman & Irigoyen | Ranunculaceae | Flowers | Methanol | - | In vitro | *T.c* | > 50 µg/ml | - | Panama | (Calderón et al., 2010) |
| Scientific name                        | Family          | Part(s) used | Solvent     | Bioactive compound | Model  | Subspecies | EC50     | CC50   | Country | References               |
|----------------------------------------|-----------------|--------------|-------------|--------------------|--------|------------|----------|--------|---------|--------------------------|
| Combretum laxum var. epiphyticum (Pittier) Croat | Combretaceae    | Aerial parts | Methanol    | -                  | In vitro | T.c        | 34 μg/ml | -      | Panama  | (Calderón et al., 2010) |
| Codonopsis pilosula var. glaberrima (Namn.) P.C.Tsoong | Campanulaceae   | Roots        | Water       | -                  | In vitro | T.c        | 20.8 μg/ml | -      | Argentina | (Schinella et al., 2002) |
| Connarus suberosus var. fulvus (Planch.) Forero | Connaraceae     | Roots woods  | Hexane      | -                  | In vitro | T.b.r      | 1.7 μg/ml | 2.6 μg/ml | Brazil   | (Charneau et al., 2016) |
| Cordia cylindrostachya (Ruz. & Pav.) Roem. & Schult. | Boraginaceae    | Leaf         | Ethanol     | -                  | In vitro | T.c        | 35 μg/ml  | -      | Panama   | (Calderón et al., 2010) |
| Crotalaria pubescens (C.Presl) C.Presl | Rosaceae        | Fruit        | Ethanol     | -                  | In vitro | T.c        | > 50 μg/ml | -      | Panama   | (Calderón et al., 2010) |
| Crotalaria morifolia (Mill.) R.M.King & H.Rob. | Asteraceae      | Fruit        | Ethanol     | -                  | In vitro | T.c        | 29 μg/ml  | -      | Panama   | (Calderón et al., 2010) |
| Curcuma aromatic L. | Zingiberaceae | Rhizome      | Water       | -                  | In vitro | T.c        | 21.4 μg/ml | -      | Argentina | (Schinella et al., 2002) |
| Cymbopogon citratus (DC.) Stapf | Poaceae         | Aerial parts | Methanol    | -                  | In vitro | T.c        | 68.2 μg/ml | -      | Mexico   | (Molina-Garza et al., 2014) |
| Dalbergia ecastaphyllum (L.) Taub. | Fabaceae        | Plant resin  | Hydroethanol | -                  | In vitro | T.c        | 88.86 μg/ml | 228.02 μg/ml | Brazil   | (Regueira-Neto et al., 2018) |
| Drimys winteri J.R.Forst. & G.Forst. | Winteraceae     | Aerial parts | DCM         | Drimenol           | In vitro | T.c        | 25.1 μg/ml | -      | Chile    | (Muñoz et al., 2013)    |
| Duguettia furfuracea (A.St.-Hil.) Saff. | Annonaceae      | Root bark    | Hexane      | -                  | In vitro | T.c        | 6.6 μg/ml | -      | Brazil   | (Mesquita et al., 2005)  |
| Eglletes viscosa var. dissecta Shinners | Asteraceae      | Whole plants | Ethanol     | -                  | In vitro | T.c        | 38 μg/ml  | -      | Panama   | (Calderón et al., 2010) |
| Ermococephala brachiata H.Rob. | Asteraceae      | Leaf         | Ethanol     | -                  | In vitro | T.c        | 33 μg/ml  | -      | Panama   | (Calderón et al., 2010) |
| Eryngium heterophyllum Engl. | Apiaceae        | Aerial parts | Methanol    | -                  | In vitro | T.c        | 11.24 μg/ml | -      | Mexico   | (Molina-Garza et al., 2014) |
| Euterpe precatoria var. longivaginata (Mart.) A.J. Hend. | Arecaceae       | Root         | Methanol    | -                  | In vitro | T.c        | > 50 μg/ml | -      | Panama   | (Calderón et al., 2010) |
| Forsythia suspensa (Thunb.) Vahl | Oleaceae        | Fruit        | Methanol    | -                  | In vitro | T.c        | 19.1 μg/ml | -      | Argentina | (Schinella et al., 2002) |
| Scientific name | Family | Part(s) used | Solvent | Bioactive compound | Model | Sub species | EC50 | CC50 | Country | References |
|-----------------|--------|--------------|---------|--------------------|-------|-------------|------|------|---------|------------|
| Fuchsia boliviana var. luxurians I.M.Johnst. | Onagraceae | Leaf | Ethanol | - | In vitro | T.c | > 50 μg/ml | - | Panama | (Calderón et al., 2010) |
| Galium latoramosum Clos | Rubiaceae | Aerial parts | Methanol | - | In vitro | T.c | > 50 μg/ml | - | Panama | (Calderón et al., 2010) |
| Gnaphalium gaudichaudianum var. gaudichaudianum | Asteraceae | Aerial parts | Methanol | - | In vitro | T.c | 36 μg/ml | - | Panama | (Calderón et al., 2010) |
| Gochnatia glutinosa (D.Don) D.Don ex Hook. & Am. | Asteraceae | Aerial parts | Methanol | - | In vitro | T.c | 20 μg/ml | - | Panama | (Calderón et al., 2010) |
| Haematoxylum brasiletto H.Karst. | Fabaceae | Bark | Methanol | - | In vitro | T.c | 7.92 μg/ml | - | Mexico | (Molina-Garza et al., 2014) |
| Haplophyllum hispanicum Spach | Rutaceae | Fruit | Ethanol | - | In vitro | T.c | 8.5 μg/ml | 16.7 | Argentina | (Schinella et al., 2002) |
| Hauga lucida Donn.Sm. & Rose | Onagraceae | Aerial parts | Methanol | - | In vitro | T.c | 32 μg/ml | - | Panama | (Calderón et al., 2010) |
| Helichrysum italicum (Roth) G.Don | Rutaceae | Aerial parts | Methanol | - | In vitro | T.c | 23.0 μg/ml | - | Argentina | (Schinella et al., 2002) |
| Himantanthus obovatus (Müll.Arg.) Woodson | Apocynaceae | Root wood | Ethanol | - | In vitro | T.c | 15.7 μg/ml | - | Brazil | (Mesquita et al., 2005) |
| Ilex guayusa Loes. | Aquifoliaceae | Leaf | Ethanol | - | In vitro | T.c | 47 μg/ml | - | Panama | (Calderón et al., 2010) |
| Inula viscosa (L.) Aiton | Asteraceae | Aerial parts | Ethanol | - | In vitro | T.c | 27.5 μg/ml | - | Argentina | (Schinella et al., 2002) |
| Ipomoea carnea subsp. carnea | Convolvulaceae | Leaf | Ethanol | - | In vitro | T.c | 48 μg/ml | - | Panama | (Calderón et al., 2010) |
| Jacaranda mimosa D.Don | Bignoniaceae | Leaf | Methanol | - | In vitro | T.c | > 50 μg/ml | - | Panama | (Calderón et al., 2010) |
| Kogenelia oblonga Ruiz & Pav. | Rosaceae | Aerial parts | Methanol | - | In vitro | T.c | 35.7 μg/ml | - | Chile | (Muñoz et al., 2013) |
| Larrea cuneifolia Cav. | Zygophyllaceae | Aerial parts | Methanol | - | In vitro | T.c | 40 μg/ml | - | Panama | (Calderón et al., 2010) |
| Lippia graveolens Kunth | Verbenaceae | Leaf | Ethanol | - | In vitro | T.c | 13 μg/ml | - | Panama | (Calderón et al., 2010) |
| Lithrea caustica Hook. & Arn. | Anacardiaceae | Aerial parts | Methanol | - | In vitro | T.c | > 50 μg/ml | - | Panama | (Calderón et al., 2010) |

(Continues)
| Scientific name                  | Family                  | Part(s) used | Solvent | Bioactive compound | Model | Subspecies | EC50    | CC50    | Country     | References                        |
|---------------------------------|-------------------------|--------------|---------|--------------------|-------|------------|---------|---------|-------------|-----------------------------------|
| Lentinus edodes L.              | Marasmiaceae            | Sclerotium   | Water   | -                  | In vitro | T.c      | 26.8 μg/ml | -       | Argentina   | (Schinella et al., 2002)          |
| Lozania pittieri (S.F.Blake) L.B.Sm. | Flacourtiaceae       | Leaf         | Methanol | -                  | In vitro | T.c      | 30 μg/ml | -       | Panama      | (Calderón et al., 2010)           |
| Lycium cuneatum Dommer          | Solanaceae              | Aerial parts | Ethanol | -                  | In vitro | T.c      | 29 μg/ml | -       | Panama      | (Calderón et al., 2010)           |
| Malanthemum paludica LaFrankie  | Convallariaceae         | Whole plants | Methanol | -                  | In vitro | T.c      | 5 μg/ml  | -       | Panama      | (Calderón et al., 2010)           |
| Mandevilla antennacea (A.DC.) K.Schum. | Apocynaceae         | Leaves stems | Ethanol | -                  | In vitro | T.c      | 100 μg/ml | -       | Bolivia     | (Fournet et al., 1994)            |
| Marrubium vulgare subsp. apulum (Ten.) H.Lind.b. | Lamiaceae           | Aerial parts | Methanol | -                  | In vitro | T.c      | 22.66 μg/ml | -       | Mexico      | (Molina-Garza et al., 2014)       |
| Matayba guianensis Aubl.        | Sapindaceae             | Stems bark   | Hexane  | -                  | In vitro | T.c      | 17.8 μg/ml | -       | Brazil      | (Mesquita et al., 2005)           |
| Miconia buxifolia Naudin        | Melastomataceae         | Leaf         | Ethanol | -                  | In vitro | T.c      | > 50 μg/ml | -       | Panama      | (Calderón et al., 2010)           |
| Mikania periplocifolia Hook. & Am. | Asteraceae             | Aerial parts | Methanol | -                  | In vitro | T.c      | > 50 μg/ml | -       | Panama      | (Calderón et al., 2010)           |
| Munnozia maronii (André) H.Rob. | Asteraceae              | Leaves       | Ethanol | -                  | In vitro | T.c      | 25 μg/ml  | -       | Bolivia     | (Fournet et al., 1994)            |
| Myrsine guianensis (Aubl.) Kuntze | Myrsinaceae            | Leaves       | Hexane  | -                  | In vitro | T.c      | 65.0 μg/ml | 107.1 μg/ml | Brazil      | (Charneau et al., 2016)           |
| Myr cyanth rhopaloides (Kunth) McVaugh | Myrtaceae              | Leaves       | Ethanol | -                  | In vitro | T.c      | 24 μg/ml  | -       | Panama      | (Calderón et al., 2010)           |
| Nicotiana glauca var. angustifolia Comes | Solanaceae            | Aerial parts | Methanol | -                  | In vitro | T.c      | 38 μg/ml  | -       | Panama      | (Calderón et al., 2010)           |
| Paeonia lactiflora var. lactiflora | Paeoniaceae            | Root         | Water   | -                  | In vitro | T.c      | 27.9 μg/ml | -       | Argentina   | (Schinella et al., 2002)          |
| Parthenium hysterophorus L.     | Asteraceae              | Leaves       | DCM     | Ambrosin           | In vitro | T.b.b    | 67.1 μg/ml | 11.46 μg/ml | Mexico      | (Sepúlveda-Robles et al., 2019)   |
| Parietaria debilis var. ceratosantha Wedd. | Urticaceae             | Aerial parts | Methanol | -                  | In vitro | T.c      | > 50 μg/ml | -       | Panama      | (Calderón et al., 2010)           |
| Scientific name                  | Family      | Part(s) used | Solvent | Bioactive compound | Model  | Sub species | EC50     | CC50 | Country | References                  |
|---------------------------------|-------------|--------------|---------|--------------------|--------|-------------|----------|------|---------|-----------------------------|
| *Paullinia clavigera* Schltdl.  | Sapindaceae | Bark         | Chloroform | -                  | In vitro | T.c         | 100%     | -    | Peru     | (González-Coloma et al., 2012) |
| *Persea americana* var.        | Lauraceae   | Leaf         | Methanol | -                  | In vitro | T.c         | 65.51 µg/ml | -    | Mexico   | (Molina-Garza et al., 2014)   |
| *Phellodendron amurense* var.  | Rutaceae    | Root bark    | Methanol | -                  | In vitro | T.c         | 11.3 µg/ml | -    | Argentina| (Schinella et al., 2002)     |
| *Phyla betulifolia* (Kunth)     | Verbenaceae | Whole plant  | Methanol | -                  | In vitro | T.c         | 30 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Phytolacca bogotensis* Kunth   | Phytolaccaceae | Aerial parts | Methanol | -                  | In vitro | T.c         | > 50 µg/ml | -    | Panama   | (Calderón et al., 2010)      |
| *Phytolacca tetramera* Hauman   | Phytolaccaceae | Aerial parts | Methanol | -                  | In vitro | T.c         | > 50 µg/ml | -    | Panama   | (Calderón et al., 2010)      |
| *Piper acutifolium* Ruiz & Pav.| Verbenaceae | Leaf         | DCM      | -                  | In vitro | T.c         | 39 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Piper aduncum var. brachyarthrum* (Trel.) Yunck. | Piperaceae | Leaf         | DCM      | -                  | In vitro | T.c         | 38 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Piper barbatum* var. andicolum* (Kunth) Trel. & Yunck. | Piperaceae | Leaf         | Ethanol  | -                  | In vitro | T.c         | 12 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Piper elongatum* var. brachyarthrum Trel. | Piperaceae | Leaf         | DCM      | -                  | In vitro | T.c         | 36 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Piper elongatum* var. brachyarthrum Trel. | Piperaceae | Leaf         | DCM      | -                  | In vitro | T.c         | 25 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Piper hirsutum* var. gamboauncum* C. DC. | Piperaceae | Leaf         | DCM      | -                  | In vitro | T.c         | 26 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Piper elongatum* var. parvispicum Yunck | Piperaceae | Root         | Ethanol  | -                  | In vitro | T.c         | 10 µg/ml  | -    | Panama   | (Calderón et al., 2010)      |
| *Piper longistylosum* C. DC.    | Piperaceae  | Leaf         | DCM      | -                  | In vitro | T.c         | > 50 µg/ml | -    | Panama   | (Calderón et al., 2010)      |
| (Continues)                     |             |              |          |                    |        |             |          |      |         |                             |
| Scientific name                     | Family              | Part(s) used | Solvent  | Bioactive compound | Model | Subspecies | EC50  | CC50  | Country | References                  |
|------------------------------------|---------------------|--------------|----------|-------------------|-------|------------|-------|-------|---------|-----------------------------|
| *Piper abalienatum* Trel.           | Piperaceae          | Leaf         | DCM      | -                 | In vitro | T.c        | 35 μg/ml | -     | Panama  | (Calderón et al., 2010)     |
| *Piper rusbyi* C. DC.              | Piperaceae          | Leaf         | DCM      | -                 | In vitro | T.c        | 32 μg/ml | -     | Panama  | (Calderón et al., 2010)     |
| *Piper scabrum* Willd. ex Kunth    | Piperaceae          | Leaf         | Ethanol  | -                 | In vitro | T.c        | 32 μg/ml | -     | Panama  | (Calderón et al., 2010)     |
| *Piper umbellatum* var. glabrum C. DC. | Piperaceae      | Leaf         | Ethanol  | -                 | In vitro | T.c        | 25 μg/ml | -     | Panama  | (Calderón et al., 2010)     |
| *Podanthus ovatifolius* Lag.       | Asteraceae          | Aerial parts | Methanol | -                 | In vitro | T.c        | 40.1 μg/ml | - | Chile   | (Muñoz et al., 2013)       |
| *Polygonum acuminatum* Kunth       | Polygonaceae        | Leaf         | Methanol | -                 | In vitro | T.c        | > 50 μg/ml | - | Panama  | (Calderón et al., 2010)     |
| *Polygonum ferrugineum* var. patagonicum (Speg.) Macloskie | Polygonaceae | Aerial parts | Methanol | -                 | In vitro | T.c        | 37 μg/ml | - | Panama  | (Calderón et al., 2010)     |
| *Poria cocos* L.                   | Polyporaceae        | Sclerotium   | Ethanol  | -                 | In vitro | T.c        | 16.8 μg/ml | - | Argentina| (Schinella et al., 2002)    |
| *Pouteria gardneri* (Mart. & Eichler ex Miq.) Baehni | Sapindaceae | Roots woods | Hexane   | -                 | In vitro | T.c        | 45.5 μg/ml | - | Brazil  | (Mesquita et al., 2005)     |
| *Pisidia carthagenensis* Jacq.     | Fabaceae            | Aerial parts | Methanol | -                 | In vitro | T.c        | 28 μg/ml | -     | Panama  | (Calderón et al., 2010)     |
| *Psidium laruo-teamum* Cambess     | Myrtaceae           | Leaves       | Hexane   | -                 | In vitro | T.b.s      | 3.9 μg/ml | >100 μg/ml | Brazil | (Charneau et al., 2016)     |
| *Pittacanthus cordatus* (Hoffmanns. ex Schult. f.) Blume | Loranthaceae | Leaf         | Ethanol  | -                 | In vitro | T.c        | 40 μg/ml | -     | Panama  | (Calderón et al., 2010)     |
| *Ranunculus sceleratus* subsp. multifidus (Nutt.) Hultén | Renonculaceae | Aerial parts | Ethanol  | -                 | In vitro | T.c        | 0.7 μg/ml | 18.7 μg/ml | Argentina| (Schinella et al., 2002)    |
| *Rauvolfia tetraphylla* L.         | Apocynaceae         | Root         | Ethanol  | -                 | In vitro | T.c        | > 50 μg/ml | - | Panama  | (Calderón et al., 2010)     |
| *Rehmania glutinosa* L.            | Oronbanchaceae      | Root         | Ethanol  | -                 | In vitro | T.c        | 24.5 μg/ml | - | Argentina| (Schinella et al., 2002)     |
| *Ruta chalepensis* L.              | Rutaceae            | Leaf         | Methanol | -                 | In vitro | T.c        | 72.30 μg/ml | - | Mexico  | (Molina-Garza et al., 2014) |

(Continues)
| Scientific name                  | Family                   | Part(s) used | Solvent | Bioactive compound | Model    | Subspecies | EC50     | CC50    | Country      | References                          |
|---------------------------------|--------------------------|--------------|---------|--------------------|----------|------------|----------|---------|--------------|-------------------------------------|
| *Salvertia convallariodora*     | Vochysiaceae             | Leaves       | Hexane  | -                  | In vitro | T.b.g      | 35.4 μg/ml | >100 μg/ml | Brazil       | (Charneau et al., 2016)             |
| (A. St.-Hil.)                   |                          |              |         |                    |          |            |          |         |              |                                    |
| *Schinus molle var. areira*     | Anacardiaceae            | Leaves       | Methanol| -                  | In vitro | T.c        | 16.31 μg/ml |         | Mexico       | (Molina-Garza et al., 2014)         |
| (L.) DC.                        |                          |              |         |                    |          |            |          |         |              |                                    |
| *Scoparia dulcis*               | Scrophulariaceae         | Whole plants | Ethanol | -                  | In vitro | T.c        | 4 μg/ml   | -       | Panama       | (Calderón et al., 2010)             |
| L.                             |                          |              |         |                    |          |            |          |         |              |                                    |
| *Scrophularia auriculata*       | Scrophulariaceae         | Aerial parts | Ethanol | -                  | In vitro | T.c        | 23.3 μg/ml | -       | Argentina    | (Schinella et al., 2002)            |
| L.                             |                          |              |         |                    |          |            |          |         |              |                                    |
| *Scutellaria baicalensis*       | Lamiaceae                | Root         | Methanol| -                  | In vitro | T.c        | 7.5 μg/ml | 28.7 μg/ml | Argentina    | (Schinella et al., 2002)            |
| f. *albiflora*                  |                          |              |         |                    |          |            |          |         |              |                                    |
| H.W.Jen & Y.J.Chang             |                          |              |         |                    |          |            |          |         |              |                                    |
| *Sebastiania brasiliensis*      | Euphorbiaceae            | Aerial parts | Methanol| -                  | In vitro | T.c        | >50 μg/ml | -       | Panama       | (Calderón et al., 2010)             |
| var. *anisophylla*              |                          |              |         |                    |          |            |          |         |              |                                    |
| Müll.Arg.                       |                          |              |         |                    |          |            |          |         |              |                                    |
| *Sebastiania commersoniana*     | Euphorbiaceae            | Aerial parts | Methanol| -                  | In vitro | T.c        | >50 μg/ml | -       | Panama       | (Calderón et al., 2010)             |
| (Baill.) L.B.Sm. & Downs        |                          |              |         |                    |          |            |          |         |              |                                    |
| *Solidago chilensis*            | Asteraceae               | Leaves       | Methanol| -                  | In vitro | T.c        | 32 μg/ml  | -       | Panama       | (Calderón et al., 2010)             |
| var. *chilensis*                |                          |              |         |                    |          |            |          |         |              |                                    |
| *Sapranthus viridiflorus*       | Annonaceae               | Aerial parts | Methanol| -                  | In vitro | T.c        | 25 μg/ml  | -       | Panama       | (Calderón et al., 2010)             |
| G.E. Schatz                     |                          |              |         |                    |          |            |          |         |              |                                    |
| *Sarcostemma gracile*           | Asclepiadaceae           | Aerial parts | Ethanol | -                  | In vitro | T.c        | 42 μg/ml  | -       | Panama       | (Calderón et al., 2010)             |
| Deccne.                         |                          |              |         |                    |          |            |          |         |              |                                    |
| *Schinus molle var. areira*     | Anacardiaceae            | Aerial parts | Methanol| -                  | In vitro | T.c        | >50 μg/ml | -       | Panama       | (Calderón et al., 2010)             |
| (L.) DC.                        |                          |              |         |                    |          |            |          |         |              |                                    |
| *Solanum actaeibotrys*          | Solanaceae               | Leaves       | Ethanol | -                  | In vitro | T.c        | 100 μg/ml | -       | Bolivia      | (Fournet et al., 1994)              |
| Rusby                          |                          |              |         |                    |          |            |          |         |              |                                    |
| *Solanum cornifolium*           | Solanaceae               | Leaf         | Ethanol | -                  | In vitro | T.c        | >50 μg/ml | -       | Panama       | (Calderón et al., 2010)             |
| Dunal                          |                          |              |         |                    |          |            |          |         |              |                                    |
| *Srevia yaconensis*             | Asteraceae               | Woods        | Ethanol | -                  | In vitro | T.c        | 50 μg/ml  | -       | Bolivia      | (Fournet et al., 1994)              |
| L.                             |                          |              |         |                    |          |            |          |         |              |                                    |
| *Styrax conterminus*            | Styracaceae              | Bark         | Ethanol | -                  | In vitro | T.c        | >50 μg/ml | -       | Panama       | (Calderón et al., 2010)             |
| Donn.Sm.                        |                          |              |         |                    |          |            |          |         |              |                                    |
| *Tabebuia serratifolia*         | Bignoniaceae             | Bark         | Hexane  | -                  | In vitro | T.c        | 100 μg/ml | -       | Peru         | (González-Coloma et al., 2012)      |
| (Vahl) G.Nicholson              |                          |              |         |                    |          |            |          |         |              |                                    |

(Continues)
| Scientific name                  | Family          | Part(s) used | Solvent | Bioactive compound | Model | Subspecies | EC50       | CC50       | Country          | References                  |
|---------------------------------|-----------------|--------------|---------|--------------------|-------|------------|------------|------------|------------------|------------------------------|
| *Tagetes caracasana* Humb. ex Wild. | Asteraceae      | Leaves       | Oil     | -                  | In vitro | T.c        | 4.56 μg/ml | 25.73 μg/ml | Brazil           | (Escobar et al., 2009)      |
| *Tagetes filifolia* subsp. filifolia | Asteraceae      | Aerial parts | Methanol | -                  | In vitro | T.c        | > 50 μg/ml | -          | Panama           | (Calderón et al., 2010)      |
| *Tagetes heterocarpha* Rydb.     | Asteraceae      | Leaves       | Oil     | -                  | In vitro | T.c        | 12.84 μg/ml | 43.03 μg/ml | Brazil           | (Escobar et al., 2009)      |
| *Tagetes lucida f. florida* (Sweet) Voss | Asteraceae      | Leaves       | Oil     | -                  | In vitro | T.c        | 18.94 μg/ml | >300 μg/ml  | Brazil           | (Escobar et al., 2009)      |
| *Tagetes zypaquirensis* Bonpl.   | Asteraceae      | Leaves       | Oil     | -                  | In vitro | T.c        | 21.30 μg/ml | 126.40 μg/ml | Brazil           | (Escobar et al., 2009)      |
| *Terminalia triflora* (Griseb.) Lillo | Combretaceae    | Aerial parts | Methanol | -                  | In vitro | T.c        | > 50 μg/ml | -          | Panama           | (Calderón et al., 2010)      |
| *Tradescantia zebrina* var. flocculosa (Gr. Brückn.) D.R. Hunt | Commelinaceae | Aerial parts | Hexane   | -                  | In vitro | T.c        | 96%       | -          | Peru             | (González-Coloma et al., 2012) |
| *Tynanthus guatemalensis* Donn.Sm | Bignoniaceae    | Stems        | Ethanol  | -                  | In vitro | T.c        | > 50 μg/ml | -          | Panama           | (Calderón et al., 2010)      |
| *Vatairea macrocarpa* var. cinerascens (Benth.) Ducke | Fabaceae        | Roots woods  | Hexane   | -                  | In vitro | T.c        | 32.6 μg/ml | >100 μg/ml  | Brazil           | (Charneau et al., 2016)      |
| *Vernonia squamulosa* Hook. & Am. | Asteraceae      | Leaves       | Petroleum | -                  | In vitro | T.c        | 100 μg/ml  | -          | Bolivia          | (Fournet et al., 1994)       |
| *Xylopia aromatica* (Lam.) Mart. | Annonaceae      | Root woods   | Hexane   | -                  | In vitro | T.c        | 21.6 μg/ml | -          | Brazil           | (Mesquita et al., 2005)      |
| *Zamia ulei* subsp. leointei (Ducke) Ducke | Zamiaceae      | Underground tuberous stem | Chloroform | -                  | In vitro | T.c        | 92.5%      | -          | Peru             | (González-Coloma et al., 2012) |
| *Zanthoxylum chloropere var. angustifolium* Engl. | Rutaceae       | Aerial parts | Alkaloidal | canthin-6-one | In vivo | T.c in Balb/c mice, 5 mg/kg/day | 80–100% inhibition | -          | Paraguay         | (Ferreira et al., 2007)      |
| *Ziziphus mistol* Griseb.        | Rhamnaceae      | Leaf         | Ethanol  | -                  | In vitro | T.c        | 25 μg/ml   | -          | Panama           | (Calderón et al., 2010)      |
| *Zuccagnia punctata* Cav.        | Fabaceae        | Leaf         | Ethanol  | -                  | In vitro | T.c        | 20 μg/ml   | -          | Panama           | (Calderón et al., 2010)      |
3.7 North America

A total of 29 plants have been identified in the literature. Interestingly, the lack of testing against T. cruzi, which is prevalent in the southern part of North America, was observed in this study. The plants showed excellent anti-trypanosomal activity with a minimum inhibitory concentration of fewer than 10 μg/ml. The crude extracts of *Nuphar luteum* (0.42 μg/ml), *Hoita macrostachya* (0.48 μg/ml) and *Rhus integrifolia* (0.50 μg/ml) showed the highest activity against *Trypanosoma brucei* (Table 6).

3.8 Oceania plants

Few studies have been found in the literature about the medicinal plants from Oceania with anti-trypanosomal activity. This corroborates with the scientometric analysis of global trypanosomiases research from 1988 to 2017 which shows that Oceania researchers have contributed less than the others to trypanosomiases research in this region (Hassan et al., 2020). Only seven plants have been identified in the literature, of which just *Corydalis crispa* (4.63 μg/ml) showed activity against *Trypanosoma brucei* (Table 7).

Many plants worldwide serve as a potential source of bioactive compounds against trypanosomiases. We encountered 77 chemically defined natural molecules reported in the literature, which have been evaluated for anti-trypanosomal activity. Fifty-nine were from Africa, 11 from Asia, 3 from Europe and 4 from Latin America. The active compounds, isolated and identified, belong to the classes of alkaloids, triterpenoids, lactones (Kohno, et al., 2010), quinoids, flavonoids, steroids, lipids, iridoids, oxygen heterocycles, benzenoids, lignans, proteids, coumarins, phenylpropanoids and peptides. The most active compounds with EC50 of <20 μg/ml are abruquinones, letestuianin, 22-hydroxysterolactone, (7,15-dihydroxy-7,15-deoxy nimb, cassythine, polyacetylenes (MS-1, MS-2 and MS-4), Putranoside A, kolavenol, triterpenoid (3β,13β-dihydroxy-urs-11-en-28-oic acid), lucidamine, oleanolic acid, phyto, betulinic acid, β-sitosterol, citronellal, clerodane, saringosterol, 24-hydroperoxy-24-vinylcholesterol, melicopicine, skimmianine, α-amyrin, punicalagin, cedrelone, vernogui-nosterol and diacetylvernoquinosterol, cynaropicrin, Schkuhrin I and II, saropeptide, oregonin, hirsutanol, curione, isoridigeranin, malahaminbe, murrayafoline, girinimbine, vanicoside E, (+)-ketopinoresinol, isorhamnetin, cardamom, onopordopicrin, juncunol, miltirone, isoobtusilactone A, canthrin-6-one, thus, are promising leads for drug development. Abruquinones K, L, A and D, artemisinin, MS-2, MS-4, dioncophylline E, dihydrochelerythrine, clerodane, Schkuhrin I, cynaropicrin, walthierones L and vanicoside E showed inhibitory activity below 1 μg/ml or 1 μM.

According to the standards of the National Cancer Institute (NCI), a crude extract can be considered active for an EC50 ≤ 20 μg/ml (Cordell et al., 1993). Hence, most plant extracts (more than 50%) showed activity below 20 μg/ml. We highlighted the plant extracts that have the most activity below 1 μg/ml, which include Kanahia laniflora, Arctium nemorosum, Crinum stuhlmanii subsp. Delagoense, Myristica fata, Narcissus broussonetii var. grandiflorus, Salvia miltiorrhiza var. carbonellii, Anthemis tintoria subsp. australis, Casearia sylvestris var. lingua, Ranunculus sceleratus subsp. Multifidus, Alnus rubra f. pinnatisecta, Anogeissus leiolepis, Coccoloba pubescens, Hoita macrostachya, Nuphar lutea subsp. Advena, Rhus integrifolia. All active extracts belong to different families and are from different parts of the plant. Hence, it was impossible to mention the particular plant parts or specific family.

Artemisinin is an endoperoxide sesquiterpene lactone isolated from Artemisia annua, one of the well-known antiparasitic and anti-tumoural chemotherapeutic agents (Rocha et al., 2005). The impacts of Artemisinin and its derivatives on Trypanosoma parasites have been investigated in in vitro and animal models. These compounds effectively inhibit the metabolism of parasites, while exhibiting limited side effects on the host (Loo et al., 2017). A large number of in vitro and in vivo studies on amastigotes, epimastigotes and trypomastigotes of Trypanosoma have displayed that artemisinin and its derivatives have pharmacological activities in controlling the parasites and have shown significant impact against protozoans such as *T. brucei rhodesiens*, *T. brucei brucei* and *T. cruzi* (Loo et al., 2017).

3.9 Critical assessment of the literature information embodied in the present study

Africa, Asia and the Middle East flore provide many promising plants, but further in vivo studies are required to confirm their application as anti-trypanosomal agents. It is worth noting that before in vivo studies, the in vitro biological activity should be accompanied by cytotoxicity studies against mammalian cells, followed by pharmacokinetic studies. On the other hand, some literature was not entered into this systematic review based on mesh terms. In West Africa and South America, *Trypanosoma vivax* is at the helm of the majority of trypanosome infections in cattle and other ruminants. This pathogen is not well established in laboratory animals, and investigation into pathogenic isolates has been restricted by the difficulty of its in vitro establishment. In this study, very few compounds were screened against *Trypanosoma vivax* (Isoun and Isoun, 1974, Cortez et al., 2006).

4 CONCLUSIONS

Many plants worldwide serve as a potential source of bioactive compounds against trypanosomiases. Africa, Asia and the Middle East flore provide many promising plants, but further in vivo studies are required to confirm their application as anti-trypanosomal agents. At the same time, the isolation of the bioactive compounds in their pure form should be pursued. Further vital investigations, including clarification of their mode of action, assessment of the efficacy of several bioactive compounds and their toxicity profile, need to be carried out.
### Table 6  Plants assessed for anti-trypanosomal application for which the EC50 values are known

| Scientific name | Family | Part(s) used | Solvent | Bioactive compound | Model | Sub species | EC50 | CC50 | Country | References |
|-----------------|--------|--------------|---------|--------------------|-------|-------------|------|------|---------|------------|
| Acer rubrum subsp. carolinianum (Walter) W.Stone | Sapindaceae | Leaf | Ethanol | - | Invitro | T.b.b | 2.88 μg/ml | - | USA | (Jain et al., 2016) |
| Alnus rubra f. pinnatisecta (Starker) Rehder | Betulaceae | Bark | Ethanol | - | Invitro | T.b.b | 0.94 μg/ml | - | USA | (Jain et al., 2016) |
| Anogeissus leiocarpus (DC.) Guill. & Perr. | Combretaceae | Root bark | Methanol | - | Invitro | T.b.b | 0.82 μg/ml | - | USA | (Kenguele, 2009) |
| Actostaphylos viscida subsp. mariposa (Dudley) PVWells | Ericaceae | Leaf | Ethanol | - | Invitro | T.b.b | 2.88 μg/ml | - | USA | (Jain et al., 2016) |
| Boykinia major var. intermedia (A. Heller) Piper | Saxifragaceae | Root | Ethanol | - | Invitro | T.b.b | 2.82 μg/ml | - | USA | (Jain et al., 2016) |
| Chrysolepis chrysophylla (Douglas ex Hook.) Hjelmq. | Fagaceae | Flowers | Ethanol | - | Invitro | T.b.b | 2.89 μg/ml | - | USA | (Jain et al., 2016) |
| Coccoloba pubescens L. | Polygonaceae | Stems | Ethanol | - | Invitro | T.b.b | 0.83 μg/ml | - | USA | (Jain et al., 2016) |
| Eriogonum fasciculatum var. pallidulum (Benth.) Torr. & A.Gray | Polygonaceae | Leaf | Ethanol | - | Invitro | T.b.b | 2.68 μg/ml | - | USA | (Jain et al., 2016) |
| Eriogonum umbellatum subsp. dumosum (Greene) S.Stokes | Polygonaceae | Leaf stems | Ethanol | - | Invitro | T.b.b | 2.79 μg/ml | - | USA | (Jain et al., 2016) |
| Eucalyptus citriodora Hook. | Myrtaceae | Leaf | Ethanol | - | Invitro | T.b.b | 2.91 μg/ml | - | USA | (Jain et al., 2016) |
| Fagara zanthoxyloides Lam. | Rutaceae | Bark | Methanol | - | Invitro | T.b.b | 6.42 μg/ml | - | USA | (Kenguele, 2009) |
| Hamamelis virginiana f. parvifolia (Nutt.) Fernald | Hamamelidaceae | Stem | Ethanol | - | Invitro | T.b.b | 2.54 μg/ml | - | USA | (Jain et al., 2016) |
| Hoita macrostachya (DC.) Rydb. | Fabaceae | Leaf | Ethanol | - | Invitro | T.b.b | 0.48 μg/ml | - | USA | (Jain et al., 2016) |
| Juniperus communis subsp. alpina (Schoop, Büchi et al.) Celok. | Cupressaceae | Leaf stem | Ethanol | - | Invitro | T.b.b | 2.40 μg/ml | - | USA | (Jain et al., 2016) |

(Continues)
| Scientific name                          | Family                  | Part(s) used | Solvent | Bioactive compound | Model   | Sub species | EC50    | CC50   | Country | References                  |
|-----------------------------------------|-------------------------|--------------|---------|--------------------|---------|-------------|---------|--------|---------|------------------------------|
| *Leea rubra* Blume ex Spreng.           | Vitaceae                | Stem         | Ethanol | -                  | In vitro| T.b.b       | 1.62 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Lepechinia calycina* var. glabella (A.Gray) Epling ex Munz | Lamiaceae                | Leaf         | Ethanol | -                  | In vitro| T.b.b       | 2.50 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Ligustrum sinense* var. myranthum (Diels) Hoefler | Oleaceae                | Leaf fruit   | Ethanol | -                  | In vitro| T.b.b       | 2.77 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Lyonia fruticosa* (Michx.) G.S. Torr.  | Ericaceae               | Stems        | Ethanol | -                  | In vitro| T.b.b       | 2.54 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Medinilla magnifica* Lindl.            | Melastomataceae         | Flowers      | Ethanol | -                  | In vitro| T.b.b       | 2.25 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Nuphar lutea* subsp. advena* Kartesz & Gandhi | Nymphaeaceae            | Fruit        | Ethanol | -                  | In vitro| T.b.b       | 0.42 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Quercus alba f. latiloba* (Sarg.) E.J.Palmer & Steyerm. | Fagaceae               | Bark         | Ethanol | -                  | In vitro| T.b.b       | 1.92 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Pseudocedrelakotschyi* (Schweinf.) Harms | Meliaceae               | Root         | Methanol| -                  | In vitro| T.b.b       | 8.94 μg/ml | -      | USA     | (Kengueule, 2009)            |
| *Rhododendron occidentale* (Torr. & A. Gray) A. Gray | Ericaceae               | Leaf         | Ethanol | -                  | In vitro| T.b.b       | 2.87 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Rhus integrifolia* (Nutt.) Benth. & Hook. f. Roth. | Anacardiaceae           | Leaf         | Ethanol | -                  | In vitro| T.b.b       | 0.50 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Ribes montigenum* McClatchie            | Grossulariaceae         | Stems        | Ethanol | -                  | In vitro| T.b.b       | 1.94 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Ribes speciosum* Pursh                  | Grossulariaceae         | Leaf stems flowers | Ethanol | -                  | In vitro| T.b.b       | 2.95 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Sabal minor* (Jacq.) Pers.              | Arecaceae               | Flowers      | Ethanol | -                  | In vitro| T.b.b       | 1.06 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Salvia spathacea* Greene                | Lamiaceae               | Stems        | Ethanol | -                  | In vitro| T.b.b       | 1.13 μg/ml | -      | USA     | (Jain et al., 2016)          |
| *Terminalia glaucescens* Planch. ex Benth. | Combretaceae            | Root         | Methanol| -                  | In vitro| T.b.b       | 9.04 μg/ml | -      | USA     | (Kengueule, 2009)            |
### TABLE 7 Plants assessed for anti-trypanosomal activity

| Scientific Name | Family | Part(s) used | Solvent | Bioactive compound | Model | Sub species | EC50 (μg/ml) | CC50 (μg/ml) | Country | References |
|-----------------|--------|--------------|---------|-------------------|-------|-------------|-------------|-------------|---------|------------|
| Aconitum laciniatum (Brühl) Stapf | Ranunculaceae | Leaf | Methanol | - | In vitro | T.b.b | >25 | >25 | Australia | (Wangchuk, 2014) |
| Ajania rubigena (Wall.) C.Shih | Compositae | Leaf | Methanol | - | In vitro | T.b.b | >10 | >10 | Australia | (Wangchuk, 2014) |
| Codonopsis bhutanica Ludlow | Campanulaceae | Leaf | Methanol | - | In vitro | T.b.b | >5 | >5 | Australia | (Wangchuk, 2014) |
| Corydalis crispa var. laeviangula C.Y.Wu & H.Chuang | Fumariaceae | Leaf | Methanol | - | In vitro | T.b.b | 4.63 | 12.5 | Australia | (Wangchuk, 2014) |
| Corydalis dubia Prain | Fumariaceae | Leaf | Methanol | - | In vitro | T.b.b | >10 | >10 | Australia | (Wangchuk, 2014) |
| Meconopsis simplicifolia (D. Don) Walp. | Papaveraceae | Leaf | Methanol | - | In vitro | T.b.b | >10 | >10 | Australia | (Wangchuk, 2014) |
| Pleurospermum amabile W. G. Craib & W.W. Sm. | Umbellifereae | Leaf | DCM | - | In vitro | T.b.b | 14.83 | >25 | Australia | (Wangchuk, 2014) |

Note: Their EC50 values are known.

### AUTHOR CONTRIBUTIONS

Shahin Nekoui: Methodology; writing – review & editing. Faham Khamesipour: Investigation; supervision; validation; writing – original draft; writing – review & editing. Pardis Mohammadi Pour: Methodology; writing – review & editing.

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

### PEER REVIEW

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### ORCID

Shahin Nekoui https://orcid.org/0000-0001-7550-6442
Faham Khamesipour https://orcid.org/0000-0003-0678-2528

Solomon Habtemariam https://orcid.org/0000-0001-6743-2244
Wanderley de Souza https://orcid.org/0000-0002-1895-1299
Pardis Mohammadpour https://orcid.org/0000-0002-2493-8293

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