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Review

Examining Natural Products with the Potential to Chagas Disease: An In-Depth Analysis

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Abstract: Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, stands as a significant public health challenge in endemic regions of the Americas. Current treatment options, limited and associated with adverse effects, underscore the need for novel therapeutic approaches. This systematic review comprehensively examines existing research on natural products as potential agents against Chagas disease. Employing a systematic search strategy across diverse databases, studies meeting predefined inclusion criteria were assessed for methodological quality and relevance. The synthesis of findings reveals a spectrum of natural products showcasing promising anti-*Trypanosoma cruzi* properties. The review discusses the limitations of current evidence, highlights gaps in knowledge, and proposes avenues for future research. By elucidating the landscape of natural products in Chagas disease treatment, this review contributes to the ongoing pursuit of innovative and accessible therapeutic strategies.

Keywords: Chagas disease; *Trypanosoma cruzi*; natural products; therapeutic approaches; anti-parasitic compounds; plant-derived compounds

Introduction

Chagas disease, also referred to as "American trypanosomiasis," is a severe health issue caused by the *Trypanosoma cruzi* parasite (MSN, n.d.). The primary vector of this disease is the triatomine bug, and the condition can be managed with antiparasitic medications, providing a ray of hope for those suffering from this debilitating disease (MSN, n.d.). While the number of Chagas disease cases has been on the rise, the exact numbers need confirmation. The data available indicates that there were approximately 6 million cases globally in 2019 [1]. This significant increase in cases emphasizes the immediate need for effective preventive and control strategies.

The Trypanosoma cruzi parasite is transmitted mainly by triatomine bugs, specifically Triatoma infestans and, to a lesser degree, Rhodnius prolixus. These bugs are predominantly found in South America, Central America, and Mexico, with their distribution varying locally based on climate, socioeconomic, and environmental factors [2]. They usually inhabit the nooks and crannies of poorly constructed houses, emerging at night to feed on human and other mammalian blood. When these bugs feed, they often defecate near the bite site, and the parasite can enter the host's body if the feces are inadvertently rubbed into the wound or a mucous membrane, such as the eye or mouth [3].

Chagas disease can manifest as an acute illness with symptoms resembling the flu, including fever, fatigue, body aches, headache, rash, loss of appetite, diarrhea, and vomiting. However, these symptoms can be mild or even non-existent, making the disease challenging to diagnose in its acute phase. It is currently endemic in 21 countries in the Americas (Paho, nd), and it affects approximately 6-7 million people worldwide annually [4]. This poses a significant public health problem, especially in rural areas where healthcare access may be restricted.

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One of the most lethal complications of Chagas disease is chronic cardiac disease. Over time, the infection can lead to inflammation and damage to the heart and nervous system, resulting in conditions such as heart failure, arrhythmias, cardiac arrest, and even death. This underscores the importance of early detection and treatment to halt the disease's progression [5].

The Trypanosoma cruzi parasite has multiple strains, referred to as discrete typing units (DTUs), which can cause varying degrees of illness in humans [6]. Some strains are more virulent than others, leading to more severe disease and complications. The triatomine bugs are the primary vectors for transmitting all strains of Trypanosoma cruzi to humans [6]. Understanding the genetic diversity of T. cruzi and its correlation with disease severity can aid in devising treatment strategies and vaccine development.

Chagas disease is a grave and escalating public health issue, particularly in the Americas. Despite the challenges, strides are being made in understanding the disease and formulating effective treatments [5]. Ongoing research, surveillance, and control measures are vital to lessen the impact of Chagas disease and enhance the quality of life of those affected [7]. With the concerted efforts of the global health community, it is hoped that we can make significant headway against this devastating disease.

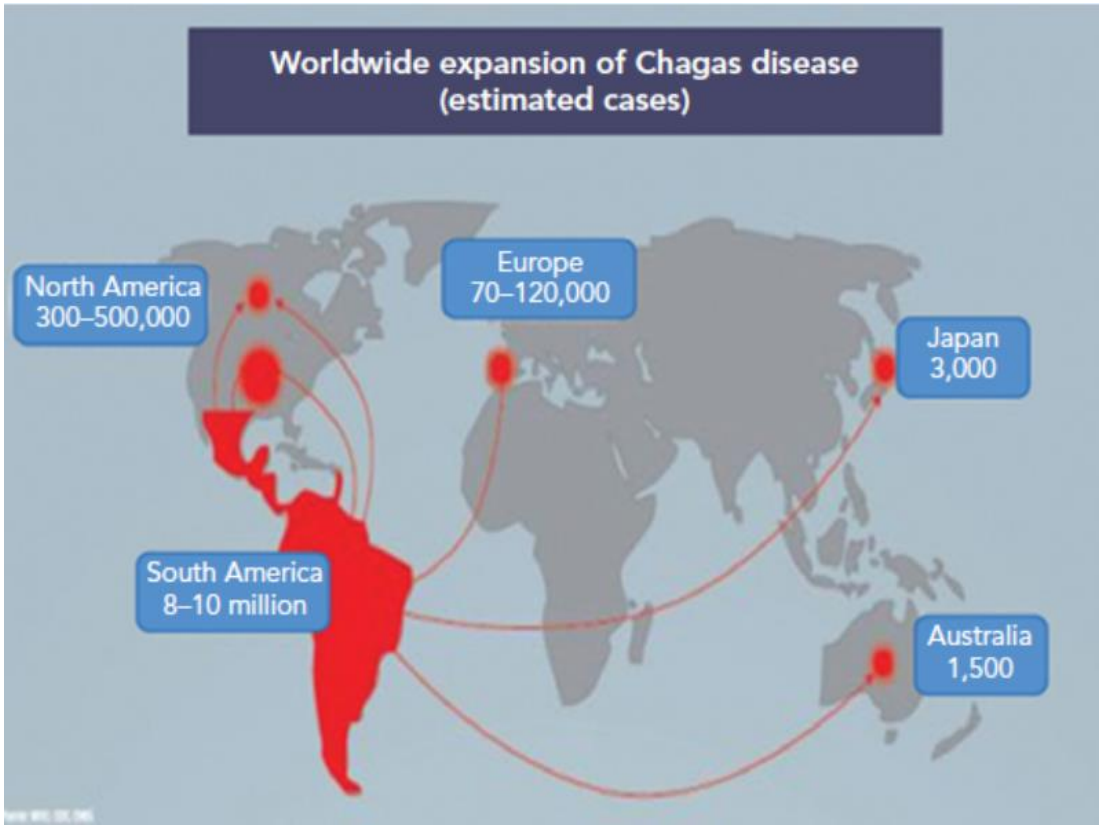

Figure 1. Worldwide expansion of Chagas disease [8].

HERBAL MEDICINE

Herbal medicine, a practice rooted in early civilizations, uses plants for medicinal purposes to treat diseases and enhance overall health and wellness. Many pharmaceutical drugs are synthesized versions of chemicals naturally found in plants. For example, the cardiac medication Digitalis was derived from the foxglove plant [7].

In relation to Chagas disease, various tribes globally use a range of herbs. Carica papaya (Caricaceae) and Euphorbia hirta (Euphorbiaceae) are two commonly used plants. Various parts of these plants, such as their leaves, roots, stems, and flowers, are used in different preparations—decoction, infusion, and leaf juice—to manage the disease [9].

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In Tamil Nadu, South India, a mix of fruits and plants is used to relieve Chagas disease symptoms. Similarly, inhabitants of Bangladesh's Lawachara Forest Reserve use an oral decoction of unripe fruits for the same purpose. In Laguna, Philippines, locals use a water infusion of Euphorbia hirta leaves and stem. Topical applications of stem barks, barks, and roots have also been reported to reduce symptoms [9].

The Santal tribe in Bangladesh's Thakurgaon District uses Azardirachtaindica (Meliaceae), while the Matigsalug tribe in Davao City, Philippines uses a decoction of the barks and bulbs of Annana reticulata and the leaves of Mentha arvensis (Lamiaceae), Synsepalumdulcificum (Sapotaceae), and Vitex negundo (Lamiaceae). The Porvenir community in India asserts that a decoction of Protium spruceanum (Burceraceae) stem bark with lemon can also effectively treat Chagas disease [9].

HERBAL MEDICINE COMPONENTS

Herbal medicine, a practice that has been in existence since the dawn of civilization, involves the utilization of different parts of plants, including leaves, stems, flowers, roots, and seeds. These components are used to formulate herbal medicines that might contain excipients like dilutions, solvents, or preservatives, as well as active substances in either their processed or raw form [10].

Herbal medicines are intricate mixtures of various molecules with complex chemical compositions. They might contain a range of components such as mucilage, essential oils, macro- and micronutrients including fats and carbohydrates, proteins, and enzymes [10].

While spices are generally dried and derived from other plant parts like seeds, bark, roots, and fruits, herbs typically refer to the leafy green or flowering parts of a plant (either fresh or dried). Herbs have a multitude of uses including culinary, medicinal, aromatherapy, and occasionally even spiritual practices [5].

In the context of Chagas disease, herbal medicines are employed to manage a variety of conditions. These include conditions like heart disease and digestive disorders, which are common complications of Chagas disease. The application of herbal medicine in treating Chagas disease attests to the adaptability and potential of these natural remedies [7].

PROBLEM STATEMENT

Chagas disease, a significant public health issue in the Americas, is caused by the Trypanosoma cruzi parasite. The primary treatment options available, mainly antiparasitic drugs, have their limitations, including side effects, inconsistent efficacy, and resistance. Despite the global impact of Chagas disease, there is a scarcity of effective and accessible treatments, especially for chronic cases. Herbal medicine, with its extensive history and variety of bioactive compounds, offers a potential avenue for new treatments. However, the potential of herbal medicine in the treatment of Chagas disease is largely untapped. This brings up a crucial question: Is it possible to identify and develop effective, safe, and accessible herbal treatments for Chagas disease? Answering this question could result in significant progress in managing Chagas disease and improving the lives of millions affected by this disease.

JUSTIFICATION

The exploration of potential herbal treatments for Chagas disease is justified by the significant global health impact of the disease, the limitations of current treatments, the potential benefits of herbal medicine, and the need for accessible and affordable therapies. This research could lead to significant advancements in the management of Chagas disease and improve the lives of those affected.

AIM

The aim of the current study is to identify several plants from various tribes across different regions that can be used for the treatment of Chagas disease and to explore the supportive therapies currently in use against this disease.

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METHOD

We carried out an extensive literature search using the phrases "Herbal medicines and Chagas disease," "Herbal treatment and Chagas disease," "Chinese herbal medicine and Chagas disease," "Plant treatment and herbal medicine," and "Chinese medicine and Chagas disease." We scoured the databases of PubMed, Google Scholar, and Research Gate for scholarly publication studies from 1987 to 2023.

Furthermore, we utilized Science Direct to perform a thorough literature search using the "with the exact phrase" category and the previously mentioned criteria. We did not reach out to the researchers, nor did we look for unpublished data. This review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. There were no limitations on the dates or terms of publication during the research projects. We also examined reference lists to find additional pertinent research.

STUDY SELECTION

The studies were chosen based on the following inclusion criteria: articles that reported the use of herbs/extracts/raw plant material in the treatment of Chagas disease; articles that detailed the mechanism of action of herbs/extracts/raw plant material that could be used to treat Chagas disease; articles that reported the use of renoprotective/nephroprotective herbs/extracts/raw plant material for Chagas disease; and articles that reported the use of renoprotective/nephroprotective herbs/extracts/raw plant material.

Any additional review articles, including systematic reviews, titles, abstracts, conference papers, editorials/letters, case reports, and submissions that did not meet the inclusion criteria, were excluded. The chosen articles were subjected to a comprehensive review to identify and exclude any pieces that did not meet the necessary criteria.

DATA EXTRACTION

In all the chosen articles, we scrutinized the year of publication, part of the plant used, chemical composition, strains of *Trypanosoma cruzi*, country, the outcome of the findings, objective, reported mechanism of action, and active constituents. The results measured in human trials were thoroughly reviewed in the articles. The complete designated evidence comprised tables and figures.

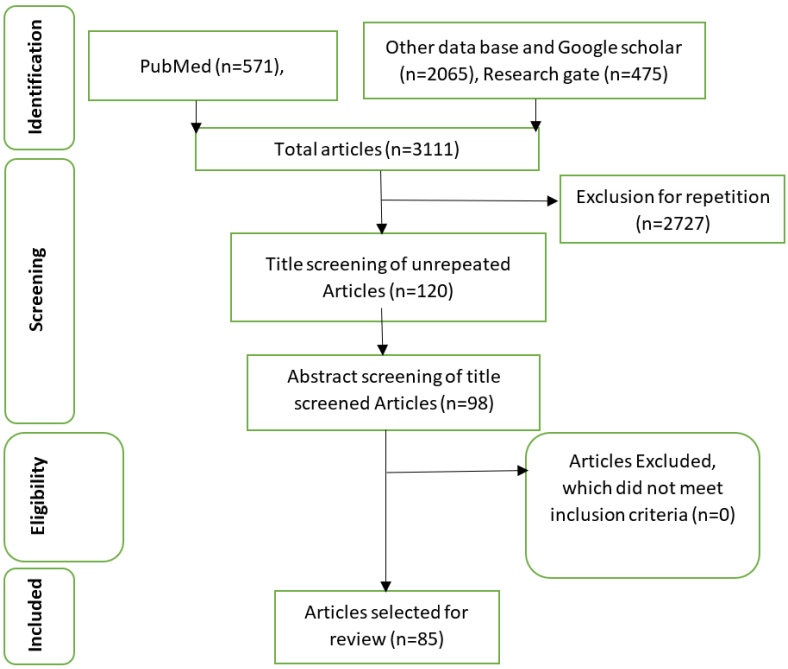

Figure 2. Flowchart of studies included in the review.

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RESULT

There are more than 85 scholarly articles that probe into the use of medicinal herbs for the treatment of Chagas disease in individuals. In this review, papers that detail the role of the evaluated herbs in treating Chagas disease are scrutinized to understand their potential contribution in fighting the disease. The Table enumerates the Plant, Aim, Chemicals/Compounds, Country, Result, and Reference of the studies.

Table.

S/N	Plant	Aim	Chemicals/Compounds	Country	Result	Reference
1	**Argemone ochroleuca, Capparis spinosa, Heliotropiumcurassavicum.**	Test plant extracts against various diseases	**Argemone ochroleuca (CHCl3 fraction), Capparis spinosa (EtOAc fraction), Heliotropiumcurassavicum (CHCl3 fraction)**	Saudi Arabia	Ten crude methanolic extracts that demonstrated potent and adequately selective antiprotozoal activity were subjected to solvent fractionation using petroleum ether, ethyl acetate and chloroform1. Only three samples showed promising antiprotozoal activity.	[11]
2	Jacalin	Test the adjuvant effect of jacalin on the mouse humoral immune response	Trinitrophenyl and Trypanosoma cruzi	Brazil	Not specified	[12]
3	Meliaceae and Rutaceae	Test the trypanocidal activity of plant extracts	C. heterophyllus and Galipeacarinata	Brazil	The results obtained from the extracts and fractions revealed that the order Rutales is a promising source for the search of new drugs for Chagas disease	[13]
4	Terminalia catappa	Test the antioxidant and antitrypano	Ellagic acid, luteolin, apigenin, and quercetin	Brazil	The ethyl acetate fraction obtained from T. catappa leaves can be an effective alternative in the	[14]

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		somal activities of extract and fractions			treatment and control of Chagas disease	
5	plant-derived sulphur-containing amides	Test the antitrypanosomal activity of plant-derived sulphur-containing amides	Sulphur-containing amides	Australia	High antitrypanosomal activity	[15]
6	Stevia satureiifolia var. satureiifolia	Test the trypanocidal and leishmanicidal activities of flavonoids	Flavonoids	Argentina	Eupatorin and 5-desmethylsinensetin showed IC50 values of 0.2 and 0.4 µg/mL on T. cruziepimastigotes and 61.8 and 75.1 µg/mL on trypomastigotes, respectively. The flavonoid 5-desmethylsinensetin showed moderate activity against T. cruzi amastigotes (IC50 value = 78.7 µg/mL) and was the most active compound on L. braziliensis promastigotes (IC50 value = 37.0 µg/mL)1. Neither of the flavonoids showed cytotoxicity on Vero cells, up to a concentration of 500 µg/mL	[16]
7	Ophiocordyceps sp.	Identify antiparasitic agents against	Leucinostatins	United states	Leucinostatin B also showed in vivo suppression of T. cruzi in a mouse model of Chagas disease	[17]

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		Trypanosoma cruzi				
8	Lippiasidoides, Lippiaoriganoidesetc	Test the trypanocidal and cytotoxic activities of essential oilsLippiasidoides, Lippiaoriganoidesetc	Essential oils from Lippiasidoides, Lippiaoriganoidesetc	Brazil	The essential oil from **Lippiasidoides** was the most effective against trypomastigotes[1]**Lippia origanoides** essential oil was the most effective against amastigotes	[18]
9	Lonchocarpuscultratus	Determine the chemical structure and anti-Trypanosoma cruzi activity of extracts	chalcones 2′,4′-dihydroxy-5′-prenylchalcone and isocordoin, the flavanone 8-prenylpinocembrin, the alkaloid 4-hydroxy-N-methylproline, the triterpenes lupeol and lupenone	Saudi Arabia	Hexanic fraction and chalcone 2′,4′-dihydroxy-5′-prenylchalcone showed potent results against human cancer cell lines tested	[19]
10	Tomato	Test if Phytomonasserpens shares antigens with Trypanosoma cruzi	Antigens	Brazil	Antigens recognized by human sera and induce protective immunity in mice	[20]
11	Lycopodium clavatum	Test the effect of Lycopodium clavatum 13c treatment on Trypanosoma cruzi infection	Lycopodium clavatum 13c.	Brazil	Beneficial immunomodulatory and neuro digestive effect	[21]

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12	Lauraceae	Test the activity of neolignans against Trypanoso ma cruzi	Neolignans	Brazil	A study on the trypanocidal activity of Brazilian plants against Trypanosoma cruzi showed potential effects of ethanol extracts obtained from Ocotea paranapiacabensis and Aegiphilalhotzkiana	[22]
13	Bertholletiaexcelsa	Test the trypanocida l activity of extracts and fractions	isolated **Betulinic acid** from the hexanic extract of Bertholletiaexcelsa	Brazil	The crude extracts and fractions of Bertholletiaexcelsa were tested against Trypanosoma cruzi. The extract CE7 was the most effective, followed by fraction F2, which also showed higher trypomastigote lysis[1]	[23]
14	**Ageratinavaccinia efolia**, **Clethra fimbriata**, **Siparunasessiliflor a**, **C. fimbriata**	Characteriz e ethanolic extracts from Colombian plants with anti-Trypanoso ma cruzi activity	Ethanolic extracts from **Ageratinavaccinia efolia**, **Clethra fimbriata**, **Siparunasessiliflor a**, **C. fimbriata**	Colo mbia	The ethanolic extracts of **Ageratinavacciniaefol ia**, **Clethra fimbriata** and **Siparunas essiliflora** showed antiprotozoal activity against epimastigotes and low cytotoxicity in mammalian cells. However, only the ethanolic extract of **C. fimbriata** showed activity against T. cruzi trypomastigotes, and it had low cytotoxicity in PBMCs. An analysis on the phytochemical composition of **C. fimbriata** extract showed5that its metabolites were primarily represented by	[24]

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					two families of compounds: **flavonoids** a nd **terpenoids**.	
15	Plant-Derived Alkaloids	Test the activity of plant-derived alkaloids against Trypanoso ma cruzi	Alkaloids	Not specif ied	The study tested the activity of these alkaloids against Trypanosoma cruzi	[25]
16	**extracts** obtained from eight different **Cerrado plant species**.	Test the activity of Brazilian Cerrado plant extract against various parasites	**ethanolic extracts** obtained from eight different **Cerrado plant species**.	Brazil	The study found that 24 out of 37 extracts showed activities against parasites: 9 with anti-P. falciparum, 4 with anti-T. cruzi and 11 with anti-T. brucei gambiense activities. High anti-protozoal activity (IC50 values < 10 µg/mL) without obvious cytotoxicity to L6 cells was observed for eight extracts from plants.	[26]
17	Drimysbrasiliensis	Test the anti-leishmanial and anti-trypanosom al potential of polygodial	Polygodial	Brazil	The crude hexane extract and polygodial showed activity against Leishmania spp. Polygodial demonstrated high parasite selectivity towards Trypanosoma cruzi trypomastigotes, with a selectivity index of 19. It also showed a leishmanicidal effect, inducing intense ultrastructural damages in Leishmania in short-time incubation.	[27]

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18	Excoecaria lucida	Test the anti-Trypanosoma cruzi activity of extracts and isolated compounds	**EL1** and **EL2**. EL1 is **ellagic acid**, and EL2 is a 1:1 mixture of **stigmasterol-3-O-β-D-glucopyranoside** and **sitosterol-3-O-β-D-glucopyranoside**.	Not specified	The EL1 and EL2 samples were more active against bloodstream trypomastigote forms of Trypanosoma cruzi, with EC50 values of 53.0±3.6 and 58.2±29.0 μg/mL, respectively[1]. At 100 μg/mL, these samples also showed 70% inhibition of L929 cells infection. Toxicity assays demonstrated that after 96 h of treatment, only the fractions Hex and EA presented detectable cytotoxicity.	[28]
19	Ursolic extracts of several plants.	Test the effect of ursolic acid-rich extract on Trypanosoma cruzi infection	Ursolic acid	Not specified	The ursolic acid-rich extract showed trypanocidal action in vitro. However, it worsened the condition of mice under experimental acute Chagas disease	[29]

S/N	Plant	Aim	Chemicals/Compounds	Country	Result	Reference
20	Alpinia	Test essential oils against Rhodniusnasutus	Essential Oils	Not specified	The essential oils and their main constituents were topically applied on R. nasutus fifth-instar nymphs. In the first 10 minutes of application, OLALPVIT and OLALPZER at 125 μg/mL provoked 73.3% and 83.3% of mortality,	[30]

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					respectively. Terpinen-4-ol at 25 µg/mL and β-pinene at 44 µg/mL provoked 100% of mortality[1]. The monitoring of resistant insects showed that both essential oils exhibited antifeedant activity	
21	Argentinean Asteraceae	Test the trypanocidal activity of sesquiterpene lactones	Sesquiterpene Lactones	Argentina	The four sesquiterpene lactones displayed trypanocidal activity on the bloodstream form of Trypanosoma cruzi. The 50% inhibitory concentration (IC50) values were 7.2 ± 0.3 µg/mL for eupatoriopicrin, 28.9±4.1 µg/mL for estafietin, 11.9 ± 4.5 µg/mL for eupahakonenin B, and 7.7 ± 0.4 µg/mL for minimolide.	[31]
22	Casearia sylvestris var. lingua	Test the trypanocidal activity of a new diterpene	Diterpene	Not specified	The study tested the trypanocidal activity of this new diterpene.	[32]
23	Lippia alba	Test the immunomodulation and antioxidant activities of	Terpenes	Colombia	The study demonstrated meaningful antioxidant and immunomodulatory activity on markers	[33]

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		major terpenes			involved in Chronic Chagasic Cardiomyopathy (CCC) pathogenesis (IFN-γ, TNF-α, IL-4, IL-10, and iNOS), which could explain their significant trypanocidal properties and their noteworthy role in preventing, and even reversing, the progression of cardiac damage in chronic Chagas disease	
24	Plants of Brazilian Restingas	Test plants with tripanocide activity against Trypanosoma cruzi strains	**quercetin**, **myricetin**, and **ursolic acid**	Brazil	All isolated substances were effective in reducing protozoal proliferation. Essentially, quercetin and myricetin did not cause mammalian cell toxicity[1]. In summary, myricetin and quercetin molecules can be used as a scaffold to develop new effective drugs against Chagas's disease	[34]
25	Zanthoxylumchiloperone	Test the trypanocidal activity of plant extracts	**limonene** and **caryophyllene oxide**	Colombia	The study demonstrated meaningful antioxidant and immunomodulatory activity on markers involved in Chronic Chagasic Cardiomyopathy	[35]

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					(CCC) pathogenesis (IFN-γ, TNF-α, IL-4, IL-10, and iNOS), which could explain their significant trypanocidal properties and their noteworthy role in preventing, and even reversing, the progression of cardiac damage in chronic Chagas disease.	
26	**medicinal plants of Bolivia**	Test the leishmanicidal and trypanocidal activities of Bolivian medicinal plants	Not specified	Bolivia	The study tested the leishmanicidal and trypanocidal activities of these Bolivian medicinal plants.	[36]
27	Muña	Test the insecticidal properties of essential oils	Essential Oils	Bolivia	The study tested the insecticidal properties of these essential oils against vectors of Chagas' disease.	[37]
28	Smallanthussonchifolius	Test the trypanocidal activity of sesquiterpene lactones	Sesquiterpene Lactones	Andes	These compounds showed a significant trypanocidal activity against the epimastigote forms of the parasite with IC50 values of 0.84 μM (enhydrin), 1.09 μM (uvedalin), and 4.90 μM (polymatin B). After a 24h treatment with 10 μg/mL of enhydrin or uvedalin, parasites were not able to	[38]

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					recover their replication rate	
29	**Canavalia ensiformis**	Test the effect of Jaburetox on Rhodniuspro lixus	Jaburetox	Brazil	The study found that Jaburetox is toxic and lethal to insects belonging to different orders when administered orally or via injection. It was observed that Jaburetox triggers a decrease in the expression of mRNA of UDP-N-Acetylglucosamine pyrophosphorylase and chitin synthetase	[39]
30	Piper jericoense	Test the activity of a furofuran lignan against Trypanosom a cruzi	Furofuran Lignan	Colom bia	The study found that the furofuran lignan showed activity both in vitro and in vivo against Trypanosoma cruzi·	[40]
31	Lychnophorapohlii	Test the trypanocidal activity of plant extracts and isolated compounds	**sesquiterpene lactones lychnopholide, centratherin, goyazensolide and 15-desoxygoyazensoli de**, and **caffeic acid** and the **flavonoids luteolin and vicenin-2**, and one active **caffeoyl quinic acid derivative**. These compounds were isolated	Brazil	The study found that the dichloromethane and methanol crude extracts from leaves plus inflorescences of Lychnophorapohlii were found to have trypanocidal activity. The bioassay-guided fractionation of the extracts yielded seven active compounds	[41]

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			from **Lychnophorapohlii**.			
32	Lychnophoragranmongolense	Test the trypanocidal and analgesic properties of the plant	**Lychnophoragranmongolense**	Brazil	The study found that the compounds showed trypanocidal and analgesic properties	[42]
33	Nectandraleucantha	Test the antitrypanosomal activity of dehydrodieugenol	Dehydrodieugenol	Brazil	The study found that dehydrodieugenol and its methylated derivative showed antitrypanosomal activity	[43]
34	Lonchocarpuscultratus	Test the anti-Trypanosoma cruzi activity of plant extracts	Compounds used were isolated from the seed of **Lonchocarpuscultratus**	Brazil	The study found that the compounds showed anti-Trypanosoma cruzi activity and cytotoxicity	[44]
35	Senna plant	Test the trypanocidal activity of (8-hydroxymethylen)-trieicosanyl acetate	(8-hydroxymethylen)-trieicosanyl acetate	Mexico	The study found that (8-hydroxymethylen)-trieicosanyl acetate showed anti-trypanosomal activity	[45]
36	Carica papaya	Test the anti-protozoal activity of crude seed extract against Trypanosoma cruzi	Seed Extract	Mexico	The study found that two doses (50 and 75 mg/kg) of the extract showed in vivo activity against the protozoan Trypanosoma cruzi. A significant reduction in the number of blood trypomastigotes was observed in animals treated with the evaluated doses of the C. papaya extract.	[46]

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37	Senna villosa	Test the trypanocidal activity of the plant in infected BALB/c mice	**chloroform extract of Senna villosa leaves**	Mexico	The study found that oral doses of 3.3, 6.6 and 13.2 μg/g were tested during 15 days on infected mice BALB/c, beginning treatment 40 days after infection to evaluate specifically the antitrypanosomal activity over the amastigote form of the parasite. In mice infected with 100 parasites, a significant reduction in the number of amastigote nests was observed in cardiac tissue of treated animals at all doses evaluated. An important reduction of amastigote nests was also observed in treated animals and infected with 500 parasites in comparison with untreated mice or mice treated with allopurinol	[47]
38	Mikania	Test the efficacy of sesquiterpene lactones against Trypanosoma cruzi and Leishmania sp.	Sesquiterpene Lactones	Argentina	The study found that mikanolide, deoxymikanolide and dihydromikanolide were active against Trypanosoma cruziepimastigotes, bloodstream trypomastigotes, and amastigotes. By	[48]

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					contrast, scandenolide was not active on Trypanosoma cruzi. Besides, mikanolide and deoxymikanolide were also active on Leishmania braziliensis promastigotes. Deoxy mikanolide presented the highest selectivity index for trypomastigotes (SI = 54) and amastigotes (SI = 12.5). In an in vivo model of Trypanosoma cruzi infection, deoxymikanolide was able to decrease the parasitemia and the weight loss associated with the acute phase of the parasite infection. More importantly, while 100% of control mice died by day 22 after receiving a lethal T. cruzi infection, 70% of deoxymikanolide-treated mice survived	
39	Cedrelafissilis	Test the trypanocidal activity of limonoids and triterpenes	Limonoids and Triterpenes	Brazil	The study found that these compounds showed trypanocidal activity	[49]

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S/N	Plant	Aim	Chemicals/Compounds	Country	Result	Reference
40	Arrabidaeatriplinervia	Test the trypanocidal activity of triterpenes	Triterpenes	Brazil	The study found that these compounds showed trypanocidal activity	[50]
41	Piper crassinervium	Test the in vitro activity of isolated compounds against Trypanosoma cruzi	The compounds studied in this research are isolated from **Piper crassinervium**	Brazil	The study found that these compounds showed activity against Trypanosoma cruzi	[51]
42	Piper regnellii	Test the activity of neolignans against Trypanosoma cruzi	Neolignans	Brazil	The study found that a series of 8.O.4′-neolignans (in their ketone, alcohol, and acetylated forms) showed interesting activities against T. cruziepimastigotes. These compounds also inhibited the in vitro differentiation of epimastigotes to trypomastigotes. When tested against HeLa cells, the same compounds did not affect the cell vitality and showed a low influence on cell viability, One of the tested compounds, compound 4 (3,4-methylenedioxi7-oxo-1′-allyl-3′,5′-dimethoxy-8.O.4′-neolignan) showed the best performance in both trypanocide and cytotoxic assays	[52]
43	Amaryllidaceae	Test the inhibitory potential of	Montanine	Ghana	The study found that montanine is a potential inhibitor of the	[53]

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		montanine against the Trypanosoma cruzi trans-sialidase enzyme			Trypanosoma cruzi trans-sialidase enzyme	
44	Delphinium staphisagria	Test the in vitro and in vivo trypanocidal activity of flavonoids	Flavonoids	Spain	The study found that these compounds showed trypanocidal activity	[54]
45	Amaryllidaceae	Test the potential of Amaryllidaceae plants for the treatment of Chagas disease	The compounds studied in this research are from a collection of **79 extracts of Amaryllidaceae plants**	Spain	The study found that two extracts, respectively from **Crinum erubescens** and **Rhodophia laandicola**, were identified as highly active and specific against **Trypanosoma cruzi** and its mammalian replicative form. The results retrieved in this study encourage further exploration of the chemical content of these extracts in search of new anti-Trypanosoma cruzi drug development starting points	[55]
46	Habranthusbrachyandrus	Test the anti-Trypanosoma cruzi activity of alkaloids	Alkaloids	Argentina	The study found that the alkaloid **ismine** was specifically active against the parasite and had low toxicity against HepG2 cells, but did not show anti-amastigote activity. The extract had specific anti-T. cruzi activity and the isolated alkaloid ismine was partially responsible for it.	[56]

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					These results encourage further exploration of H. brachyandrus alkaloids in search of novel starting points for Chagas disease drug development	
47	Anacardium occidentale	Test the inhibitory activity of compounds against Trypanosoma cruzisirtuins	**Two derivates of cardol (1, 2), cardanol (3, 4), and anacardic acid (5, 6)** isolated from **cashew nut (Anacardium occidentale, L. Anacardiaceae)**	Brazil	The study found that the two anacardic acids (5, 6) inhibited both TcSir2rp1 and TcSir2rp3, while the cardol compound (2) inhibited only TcSir2rp1. The most potent sirtuin inhibitor active against the parasite was the cardol compound (2), with an EC50 value of 12.25 μM, similar to that of benznidazole. Additionally, compounds (1, 4), which were inactive against the sirtuin targets, presented anti-T. cruzi effects[1]. In conclusion, the results showed the potential of Anacardium occidentale compounds for the development of potential sirtuin inhibitors and anti-Trypanosoma cruzi agents	[57]
48	Physalis angulata	Test the in vitro and in vivo antiparasitic activity of concentrated ethanolic extract	Ethanolic Extract	Brazil	The study found that the extract effectively inhibits the epimastigote growth and reduces bloodstream trypomastigote viability. It causes parasite cell death by necrosis. The extract impairs parasite infectivity as well as amastigote development in concentrations noncytotoxic	[58]

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					to mammalian cells. In mice acutely-infected with T. cruzi, the extract reduced the blood parasitaemia. When combined with benznidazole, the extract showed a synergistic anti-T. cruzi activity	
49	**Pterodonpubescens seeds**	Test the trypanocidal activity of geranylgeraniol	Geranylgeraniol	Brazil	The study found that GG-OH showed similar potency to PF1.2, while the oleaginous extract from P. pubescens seeds and the other fractions were about three times less active.	[59]
50	Arrabidaeachica	Test the photodynamic inactivation of Trypanosoma cruzi by pheophorbide a	Pheophorbide a	Brazil	**Pheophorbide a** compound had activity against the protozoan in the presence of light and caused morphological and ultrastructural changes, demonstrating its potential in photodynamic therapy.	[60]
51	Asteraceae	Test the potential of Asteraceae plants against Leishmaniasis and Chagas Disease	Ferulic acid, Rosmarinic acid, and Ursolic acid from Baccharisuncinella DC., Deoxymikanolide from Mikania micrantha, and (+)-15-hydroxy-labd-7-en-17-al from Aristeguietiaglutinosa Lam	Brazil	The study found that these compounds were effective in treating experimental leishmaniasis and showed in vivo anti-T. cruzi action. It was highlighted that these compounds may help in the development of new effective agents against these neglected diseases.	[61]
52	Pentacaliadesiderabilis (Vell.)	Test the anti-	Jacaranone	Brazil	The study found that jacaranone showed activity	[62]

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	Cuatrec. (Asteraceae)	malarial, anti-trypanosomal, and anti-leishmanial activities of jacaranone			against promastigotes of Leishmania (L.) chagasi, Leishmania (V.) braziliensis, and Leishmania (L.). amazonensis showing an IC50 of 17.22, 12.93, and 11.86 µg/mL, respectively. Jacaranone was also tested in vitro against the Trypanosoma cruzi trypomastigotes and Plasmodium falciparum chloroquine-resistant parasites (K1 strain) showing an IC50 of 13 and 7.82 µg/mL, respectively, and was 3.5-fold more effective than benznidazole in anti- Trypanosoma cruzi assay. However, despite the potential against promastigotes forms, this compound was not effective against amastigotes of L. (L.) chagasi and T. cruzi.	
53	Lippia alba	Test the anti-Trypanosoma cruzi activity of essential oils and their major terpenes	Essential Oils, Terpenes	Colombia	The study found that these oils or their bioactive terpenes (citral, caryophyllene oxide and limonene) could be inducing T. cruzi cell death by an apoptotic-like mechanism. Citral, caryophyllene oxide, and limonene showed a possible induction of an apoptotic-like phenotype	[63]
54	Anacardium occidentale	Test the trypanocidal activity of the	The compounds studied were essential/volatile oils (EOs) from	Brazil	The study found that all the tested oils showed an inhibitory effect on the growth and survival of all	[64]

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		chemical constituents of Anacardium occidentale	various plants. The main constituents of EOS were: δ-cadinene (15.88%), trans-caryophyllene (9.77%) e α-Muurolol (9.42%) for EBEO; trans-caryophyllene (15.24%), bicyclogermacrene (7.33%) e cis-calamenene (7.15%) for HFEO; trans-caryophyllene (30.91%), caryophyllene oxide (13.19%) and spathulenol (5.68%) for HPEO; Xanthoxylin (17.20%) trans-caryophyllene (14.34%) and methyl-eugenol (5.60%) for HSEO; Thymol (49.81%), carvacrol (31.6%) and σ-cimene (10.27%) for LMEO and octanoic acid (38.83%) dodecanoic acid (38.45%) and		forms of T. cruzi and moderate cytotoxicity towards the mammalian cells (100 < CC 50 < 9500 μg/mL)	

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			decanoic acid (20.51%) for SCEO			
55	Clethra fimbriata	Test the anti-Trypanosoma cruzi activity of a terpenoid-rich extract	Terpenoid-rich Extract	Heliyon	The study found that the Clethra fimbriata hexane extract exhibited the highest activity capable of inhibiting the three parasite developmental stages with an IC50 /EC50 of 153.9 ± 29.5 (epimastigotes), 39.3 ± 7.2 (trypomastigotes), and 45.6 ± 10.5 (amastigotes) µg/mL, presenting a low cytotoxicity in VERO cells with a selectivity index ranging from 6	[65]
56	Camellia sinensis	Test the anti-Trypanosoma cruzi activity of catechins	Catechins	Not specified	The study found that the purified compounds lysed more than 50% of the parasites present in the blood of infected BALB/c mice at concentrations as low as 0.12 to 85 pM. The most active compounds were gallocatechin gallate and epigallocatechin gallate, with minimal bactericidal concentrations that inhibited 50% of isolates tested of 0.12 and 0.53 pM, respectively[1]. **Country**: The country where the research was conducted is not mentioned in the available snippets.	[66]

S/N	Plant	Aim	Chemicals/ Compounds	Country	Result	Reference
57	Cichoriumintybus	Test the anti-	The study revealed 11	Not specified	All C. intybus	[67]

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		protozoal activity against Trypanosoma cruzi	compounds in C. intybus leaves strongly linked with activity against trypomastigotes, including the sesquiterpene lactone lactucin, and flavonoid- and fatty acid-derivatives. Furthermore, seven distinct C. intybus molecules (including two sesquiterpene lactone-derivatives) were predicted to be involved in reducing the number of mammalian cells infected with amastigotes		extracts induced concentration-dependent effects against T. cruzi trypomastigotes. C. intybus leaf extracts had higher trypanocidal selectivity and lower cytotoxicity on mammalian cells than root extracts. The leaf extract of C. intybus cv. Goldine also significantly reduced the number of mammalian cells infected with T. cruzi amastigotes	

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58	Crithmummaritimum	Test the in vitro anti-Trypanosoma cruzi activity	The study involved testing decoctions, tinctures, and essential oils from everlasting's flowers and sea fennel's stems, leaves, and flowers against intracellular amastigotes of two T. cruzi strains	Portugal	The extract from the sea fennel flower decoction displayed significant anti-trypanosomal activity and no toxicity towards the host cell (EC50 = 17.7 µg/mL, selectivity index > 5.65). Subsequent fractionation of this extract afforded 5 fractions that were re-tested in the same model of anti-parasitic activity	[68]
59	Tabebuia	Study the chemical reactivity of naphthoquinones with anti-trypanoso	Naphthoquinones	Not specified	The study found that among the cyclofunctionalised products the oxazolic and imidazolic	[69]

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		mal efficacy			derivatives showed ± 1.5 to 34.8 times higher activity than crystal violet, the standard drug for the sterilization of stored blood	
60	Senna villosa, Serjaniayucatanensis, Byrsonimabucidaefolia, and Bourreria pulchra.	Test the in vitro and in vivo trypanocidal activity of medicinal plants	The compounds studied were ethanol extracts of the aforementioned plants	Mexico	The leaf extracts of S. yucatanensis and B. pulchra were the most active against epimastigotes (IC 100 = 100 µg/mL) and trypomastigotes of T. cruzi (95% or more reduction in the number of parasites at 100 and 50 µg/mL). However, only the leaf extract of S. yucatane	[70]

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					nsis showed significant trypanocidal activity when tested in vivo, reducing 75% of the parasitemia in infected mice at 100 mg/kg	
61	Moringa oleifera	Test the cytotoxicity of a trypsin inhibitor from the flower extract against Trypanosoma cruzi	Trypsin Inhibitor	The research was conducted in affiliation with multiple institutions, including the Departamento de Bioquímica, Centro de Biociências, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil; Departamento de Imunologia, Centro de PesquisasAggeuMagalhães, Fundação Oswaldo Cruz, Recife, Pernambuco, Brazil; and Departamento	Both the extract and the trypsin inhibitor caused lysis of T. cruzi trypomastigotes with LC50/24 h of 54.18 ± 6.62 and 41.20 ± 4.28 µg/mL, respectively. High selectivity indices (7.9 to >12) for T. cruzi cells over murine peritoneal macrophages and Vero cells were found for the extract and the	[71]

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				de Morfologia e Fisiologia Animal, Universidade Federal Rural de Pernambuco, Recife, Brazil.	trypsin inhibitor	
62	Lippia alba	Test the immunomodulatory, trypanocide, and antioxidant properties of essential oil fractions	Essential Oil Fractions	The research was conducted in affiliation with multiple institutions, including the Departamento de Microbiologia, Instituto AggeuMagalhães IAM-FIOCRUZ/PE, Av. MoraesRego s/n, Campus da UFPE, 50670-420 Pernambuco, Brazil	The study found that limonene-enriched (ACT1) and citral/caryophyllene oxide-enriched (ACT2) essential oils fractions derived from Carvone and Citral-L. alba chemotypes, respectively, exhibit similar trypanocidal effects to Benznidazole (BZN), against amastigotes. Synergistic antiparasitic activity was	[72]

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					observed when ACT1 was combined with BZN or ACT2. ACT1 also decreased the oxidative stress, mitochondrial metabolism, and genotoxicity of the therapies. The ACT1 + ACT2 and ACT1 + BZN experimental treatments reduced the pro-inflammatory cytokines (IFN-γ, IL-2, and TNF-α) and increased the anti-inflammatory cytokines (IL-4 and IL-10)	

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63	*Castanedias antamartensis*	Test the trypanocidal effect of alcoholic extract	Alcoholic Extract	Not specified	Not specified	[73]
64	Ambrosia species.	Test the in vitro and in vivo trypanocidal activity of four terpenoid derivatives	Terpenoid Derivatives	Not specified	The compounds cumanin and cordilin were found to be active against Trypanosoma cruziepimastigotes, showing 50% inhibition concentrations (IC 50) values of 12 µM and 26 µM, respectively. These compounds were also active against bloodstream trypomastigotes, regardless of the T. cruzi strain tested. Psilostachyin and cumanin	[74]

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					were also active against amastigote forms with IC 50 values of 21 μM and 8 μM, respectively	
65	**Calophyllumbrasiliense** and **Mammeaamericana** (Clusiaceae)	Test the trypanocidal activity of mammea-type coumarins	Mammea-type Coumarins	Mexico	The most potent compounds were mammea A/BA, A/BB, A/AA, A/BD and B/BA, with MC100 values in the range of 15 to 90 g/ml. Coumarins with a cyclized ,-dimethylallyl substituent on C-6, such as mammea B/BA, cyclo F + B/BB cyclo F, and isomammeigin, showed MC100	[75]

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					values > 200 g/ml	
66	Pinus oocarpa	Test the trypanocidal activity of oleoresin and terpenoids	Oleoresin, Terpenoids	Korea	Two hits satisfied the selection criteria and were escalated to molecular dynamics simulation and binding free energy calculations. These hits demonstrated higher dock scores, displayed interactions with the key residues portraying an ideal binding mode complemented by mapping to all the features of pharm 1 and pharm 2. Additionally, they rendered stable root mean square	[76]

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					deviation (RMSD) and potential energy profiles, illuminating their potentiality as prospective antichagastic agents	
67	The study involved numerous plants as sources of natural products	Review the potential of natural products from plants as drug candidates and lead compounds against leishmaniasis and trypanosomiasis	The compounds investigated were various plant-derived natural products from different structural classes, including various alkaloids, terpenoids, flavonoids, and quinonoids.	Not specified	Given the activities of these agents and their diverse range of effects on parasite biology, natural products are a potentially rich source of drug candidates and leads against leishmaniasis and trypanosomiasis	[77]
68	Quechua, Izoceño-Guaraní, Chiquitano, and Ayoreo	Review the phylobioactive hotspots in plant	The study does not mention the names of the specific	Bolivia	**Result**: The study systematically uncovers	[78]

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		resources used to treat Chagas disease	compounds used. However, it mentions the bioprospecting of natural product classes effective against Trypanosoma cruzi		antichagasic phylogenetic hotspots in the plant kingdom as a potential resource for drug discovery based on ethnopharmacological hypotheses	
69	Salvia gilliessi	Test the trypanocidal activity of a novel icetexane diterpene	Icetexane Diterpene	Not specified	The result of the research was that 5-epi-icetexone from Salvia gilliessi is active against Trypanosoma cruzi	[79]

S/N	Plant	Aim	Chemicals/Compounds	Country	Result	Reference
70	Eugenia uniflora	Test the anti-Trypanosoma cruzi activity	**ethanolic extract** from E. uniflora	Brazil	The results demonstrated that E. uniflora has anti-Trypanosoma activity. The concentration presenting 50% of activity (EC50) was 62.76 µg/mL, and the minimum inhibitory	[80]

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					concentration (MIC) was ≤1024 µg/mL	
71	Syzygiumaromaticum and Zingiber officinale	Test the anti-Trypanosoma cruzi activity of essential oils, alone or in combination with benznidazole	essential oils from **Syzygiumaromaticum** (clove) and **Zingiber officinale** (ginger), and **benznidazole**	Brazil	The results showed that clove and ginger essential oils, administered alone and in combination with benznidazole, promoted suppression of parasitemia ($p < 0.0001$), except for the animals treated with CEO alone, which presented a parasitemia curve similar to untreated animals	[81]
72	Pfaffiaglomerata	Test the in vitro activities of root extract and its hydrolyzed fractions	Root Extract, Hydrolyzed Fractions	Not Specified	The results showed that fractions F2 and F3 exhibited moderate activity, and pfaffic acid, one of the main chemical constituents of these fractions, displayed IC50 = 44.78 µm (21.06 µg/ml). On the other hand, the hydroalcoholic extract of	[82]

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					P. glomerata roots, which is rich in pfaffosides, was inactive	
73	South American Vernonieae	Test the trypanocidal activity of extracts and sesquiterpene lactones	Extracts, Sesquiterpene Lactones		The results showed that fractions F2 and F3 exhibited moderate activity, and pfaffic acid, one of the main chemical constituents of these fractions, displayed IC50 = 44.78 μm (21.06 μg/ml). On the other hand, the hydroalcoholic extract of P. glomerata roots, which is rich in pfaffosides, was inactive	[83]
74	Genipaamericana	Test the trypanocidal activity of polysaccharide extract from leaves	Polysaccharide Extract	Brazil	The results showed that PFI had an effect against epimastigote forms (EC 50/24 h = 580 ± 0.17 μg/ml; EC 50/48 h = 530 ± 0.13 μg/ml; EC 50/72 h = 500 ± 0.14 μg/ml), while PFII did not show effect on any	[84]

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					tested concentrations. I n trypomastigotes, the PFI and PFII showed effect with EC 50 values of 100 ± 0.09 and 23 ± 0.06 μg/ml respectively. PFI and PFII were also able to decrease amastigotes/100 cells parameter. PFI and PFII were not cytotoxic in LLC-MK2 cells at the highest tested concentration, resulting in selectivity index (SI) higher than 15 for PFI and higher than 65 for PFII	
75	Psilostachyin C that can be found in several plants	Test the trypanocidal activity of psilostachyin C	Psilostachyin C	Not specifi ed	The results showed that Psilostachyin C may be considered a promising template for the design of novel trypanocidal agents. In addition, Psilostachyin C inhibited the	[85]

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					growth of Leishmania mexicana and Leishmania amazonensis promastigotes. The IC(50) values were 1.2 μg/mL and 1.5 μg/mL, respectively	
76	Ambrosia spp	Test the mode of action of the sesquiterpene lactones psilostachyin and psilostachyin C	Sesquiterpene Lactones	Argentina	The results showed that both sesquiterpene lactones were capable of interacting with hemin[1]. Psilostachyin increased about 5 times the generation of reactive oxygen species in Trypanosoma cruzi after a 4h treatment, unlike psilostachyin C which induced an increase in reactive oxygen species levels of only 1.5 times	[86]
77	Lychnophorastaa vioides	Test the trypanocidal activity of extracts	Extracts	Not specified	The result of the study was that Lychnophorastaa vioides Mart. (Vernoniea e, Asteraceae) showed trypanocidal activity	[87]

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78	Not specified	Review the potential therapeutic use of herbal extracts in trypanosomiasis	Herbal Extracts	Not specified	Not specified	[88]
79	Smallanthus sonchifolius	Test the trypanocidal activity of germacranolide-type sesquiterpene lactones	Germacranolide-type Sesquiterpene Lactones	Argentina	The three compounds exhibited leishmanicidal activity on both parasite forms with IC 50 values of 0.42–0.54 μg/ml for promastigotes and 0.85–1.64 μg/ml for intracellular amastigotes. Similar results were observed on T. cruziepimastigotes (IC 50 0.35–0.60 μg/ml). The TEM evaluation showed marked ultrastructural alterations, such as an intense vacuolization and mitochondrial swelling in both L. mexicana promastigotes and T. cruziepimastig	[89]

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					otes exposed to the STLs	
80	cashew nut (Anacardium occidentale)	Study the differential lethal action of C17:2 and C17:0 anacardic acid derivatives in Trypanosoma cruzi	Anacardic Acid Derivatives	Not specified	Found a differential lethal action of the two anacardic acid derivatives in Trypanosoma cruzi	[90]
81	Garlic	Test the inhibition of phosphatidylcholine biosynthesis and cell proliferation in Trypanosoma cruzi by ajoene	Ajoene	Not specified	The result of the research was that ajoene inhibited phosphatidylcholine biosynthesis and cell proliferation in Trypanosoma cruzi	[91]
82	Extracts of Colombian plants	Test the trypanocidal activity of extracts of Colombian plants	Extracts	Colombia	Not specified	[92]
83	Aristeguietiaglutinosa	Test the in vitro and in vivo trypanocidal activity of extracts and active principles	Extracts, Active Principles	Uruguay	Both the hydro-ethanolic extract and the isolated active principle, (+)-15-hydroxy-7-labden-17-al, showed anti-Trypanosoma cruzi activity in vivo. They were well tolerated by mice and no secondary side	[93]

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					effects were observed	
84	Piper	Test the anti-Trypanosoma cruzi activity of piperovatine and piperlongumine	Piperovatine, Piperlonguminine	Brazil	Both piperovatine and piperlonguminine showed antitrypanosomal activity against epimastigotes and intracellular amastigotes of Trypanosoma cruzi. They caused severe alterations in T. cruzi, mainly located in the plasma membrane and mitochondria, which might trigger biochemical alterations that lead to cell death	[94]
85	A. scabra & A. elatior	Test the brine shrimp lethality assay as a prescreening system for anti-Trypanosoma cruzi activity	The compounds investigated were the sesquiterpene lactone (STL) cumanin isolated from A. elatior and two other STLs, psilostachyin and cordilin, and one sterol glycoside, daucosterol, isolated from A. scabra	Not specified	The compounds cumanin and cordilin were found to be active against Trypanosoma cruziepimastigotes, showing 50% inhibition concentrations (IC 50) values of 12 μM and 26 μM, respectively. These compounds were also active	[95]

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					against bloodstrean trypomastigotes, regardless of the T. cruzi strain tested. Psilostachyin and cumanin were also active against amastigote forms with IC 50 values of 21 μM and 8 μM, respectively	

Figure: Digital Illustration of Trypanosome Parasites in Blood which is causing Chagas Disease [96].

DISCUSSION

This study examines some crucial plants used in the treatment of Chagas disease [97]. Essential oils from *Alpinia zerumbet* and *A. vittata* have exhibited significant trypanocidal activity against *Rhodnius nasutus*, a vector of Chagas disease [2]. Four sesquiterpene lactones isolated from species of Asteraceae have shown trypanocidal activity [55]. A newly discovered diterpene from *Casearia sylvestris* var. lingua has exhibited trypanocidal activity [3]. The primary terpenes from *Lippia alba* essential oils have demonstrated trypanocidal and cardioprotective mechanisms in an experimental model of Chronic Chagas Disease [9]. Plants from Brazilian restingas have shown tripanocidal activity against *Trypanosoma cruzi* strains [4]. The leaf extract of *Zanthoxylum chiloperone* has been identified as the first sustainable treatment for Chagas disease [6]. Several medicinal plants from Bolivia have shown leishmanicidal and trypanocidal activities [5]. The essential oils of muña, Bolivian plants traditionally used as pesticides, have shown insecticidal properties against vectors of Chagas' disease [7]. The active sesquiterpene lactones from *Smallanthus sonchifolius* have shown trypanocidal activity [9]. Jaburetox has affected gene expression and enzyme activities in *Rhodnius prolixus*, a vector of Chagas' disease [98]. A furofuranlignan isolated from *Piper jericoense* has shown activity in vitro and in vivo against *Trypanosoma cruzi* [4]. Chemical constituents of Lychnophora plants have shown trypanocidal activity against *Trypanosoma cruzi* strains [6]. Sesquiterpene lactones isolated from species of Mikania plants have shown potential efficacy against *Trypanosoma cruzi* and Leishmania sp. [5]. Limonoids and triterpenes from *Cedrela fissilis* have shown trypanocidal activity [7]. This plant contains triterpenes that have shown trypanocidal activity [9]. Compounds isolated from *Piper crassinervium* have demonstrated in vitro activity against *Trypanosoma cruzi* [10]. Jacaranone, an alkaloid isolated from *Pentacalia desiderabilis*, has shown anti-malarial, anti-trypanosomal, and anti-leishmanial activities [6]. The seed oil of *Pterodon pubescens*, particularly a component called geranylgeraniol, has shown anti-*Trypanosoma cruzi* activity [5]. These plants are considered a

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potential natural resource for the treatment of Chagas disease. In particular, the Amaryllidaceae alkaloid, montanine, is a potential inhibitor of the *Trypanosoma cruzi* trans-sialidase enzyme [7]. Alkaloids isolated from *Habranthus brachyandrus* have shown anti-*Trypanosoma cruzi* activity [9]. Compounds from *Anacardium occidentale* have been found to inhibit *Trypanosoma cruzisirtuins* [10]. The concentrated ethanolic extract of *Physalis angulata* has shown in vitro and in vivo antiparasitic activity against *Trypanosoma cruzi* [6]. A terpenoid-rich extract from *Clethra fimbriata* exhibits anti-*Trypanosoma cruzi* activity and induces T cell cytokine production [5]. Catechins from *Camellia sinensis* (Green Tea) have shown anti-*Trypanosoma cruzi* activity [7]. *Cichoriumin tybus* L This plant was studied for its anti-protozoal activity and metabolomic analyses against *Trypanosoma cruzi* [9]. Sea Fennel (*Crithmum maritimum* L.) This halophyte from Southern Portugal was investigated for its in vitro anti-*Trypanosoma cruzi* activity [10]. Synthetic heterocyclic derivatives of active quinones from *Tabebuia* sp were evaluated for their trypanocidal activity [6]. The flower extract of *Moringa oleifera* was found to be cytotoxic to *Trypanosoma cruzi* with a high selectivity over mammalian cells [71]. The alcoholic extract of the leaves of *Castanedias antamartensis* was found to have a trypanocidal effect based on altered mitochondrial function [73]. A potent HPK1 inhibitor from *Salvia gilliessi* may promote T-cell response to tumors through various mechanisms that enhance T-cell function in the cancer immunity cycle [99]. *Eugenia uniflora* has demonstrated anti-*Trypanosoma cruzi* and cytotoxic activities [80]. Essential oils from *Syzygium aromaticum* and *Zingiber officinale*, administered alone or in combination with benznidazole, were found to reduce the parasite load in mice orally inoculated with *Trypanosoma cruzi* II [81]. The root extract of *Pfaffia glomerata* and its hydrolyzed fractions, along with Pfaffic Acid, showed in vitro activities against *Trypanosoma cruzi* Trypomastigotes [82]. Germacranolide-type sesquiterpene lactones from *Smallanthus sonchifolius* exhibited promising activity against *Leishmania mexicana* and *Trypanosoma cruzi* [89]. *Lychnophora staavioid*es Mart (Vernonieae, Asteraceae) demonstrated trypanocidal activity [87]. The polysaccharide extract from the leaves of *Genipa americana* showed trypanocidal activity [84]. Extracts from South American Vernonieae (Asteraceae) plants and their sesquiterpene lactones exhibited trypanocidal activity [83].

Abdel-Sattar et al. (2010) [11] investigated the in vitro activity of methanol extracts from 51 plants collected from Saudi Arabia against *Plasmodium falciparum*, *Trypanosoma brucei*, *T. cruzi* and *Leishmania infantum*. Albuquerque et al. (1999) [12] evaluated the trypanocidal activity of plant extracts from the Meliaceae and Rutaceae families. Araújo et al. (2023) [14] studied the antioxidant and antitrypanosomal activities of extracts and fractions obtained from *Terminalia catappa*. Astelbauer et al. (2010) [15] reported on the high antitrypanosomal activity of plant-derived sulphur-containing amides. Beer et al. (2016) [16] isolated flavonoids from *Stevia satureiifolia* var. satureiifolia and tested their trypanocidal and leishmanicidal activities. Bernatchez et al. (2022) [17] identified Leucinostatins from *Ophiocordyceps* sp. as antiparasitic agents against *Trypanosoma cruzi*. Borges et al. (2012) [18] evaluated the trypanocidal and cytotoxic activities of essential oils from medicinal plants in Northeast Brazil. Bortoluzzi et al. (2021) [19] determined the chemical structure and anti-*Trypanosoma cruzi* activity of extracts from the roots of *Loncho carpuscultratus*. Bosch-Navarrete et al. (2023) [100] studied the activity of Strasseriolides against *Trypanosoma cruzi*. Breganó et al. (2003) [20] reported that *Phytomonas serpens*, a tomato parasite, shares antigens with *Trypanosoma cruzi* that are recognized by human sera and induce protective immunity in mice. Cabral et al. (2010) [22] studied the anti-*Trypanosoma cruzi* activity of neolignans from plants in northeastern Brazil (Lauraceae). Campos et al. (2005) [23] evaluated the trypanocidal activity of extracts and fractions of *Berthol letiaexcelsa*. Canavaci et al. (2010) [101] developed in vitro and in vivo high-throughput assays for testing anti-*Trypanosoma cruzi* compounds. Castañeda et al. (2021) [24] conducted a preliminary chemical characterization of ethanolic extracts from Colombian plants with promising anti-*Trypanosoma cruzi* activity. Corrêa et al. (2011) [26] reported on the anti-leishmanial activity of polygodial isolated from stem barks of *Drimysbrasiliensis miers* (Winteraceae). da Silva et al. (2018) [28] studied the anti-*Trypanosoma cruzi* activity of extracts and fractions from *Excoecaria lucida* leaves. Daga et al. (2023) [29] reported that ursolic acid-rich extract showed trypanocidal action in vitro but worsened mice under experimental acute Chagas disease.

Benefits, Drawbacks and Limitations.

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Herbal medicine, a fundamental aspect of traditional healing methods, has demonstrated considerable potential in treating Chagas disease, a tropical parasitic disease caused by the *Trypanosoma cruzi* [55]. A large proportion of drugs used worldwide in clinical settings are derived from natural substances, underscoring the potency and potential of nature's pharmacy [3].

Herbs are not merely supplementary therapies; they also interact positively with prescription medications, providing a synergistic effect that can enhance the overall treatment outcome [102]. This interaction, known as herb-drug interaction, can potentially enhance the effectiveness of the treatment and decrease the dosage of the prescription medication, thereby reducing its side effects [102].

The science behind the use of herbs was enigmatic until recently. However, due to dedicated research using herbs to treat various diseases, the mechanisms are now becoming more transparent [3]. This has led to a better understanding of how these natural remedies function and how they can be utilized for the benefit of patients. For example, the active ingredients in herbs can interact with biological targets in our body, modulating physiological functions and providing therapeutic effects [3].

Despite the advantages, the use of herbal medicine is not without its disadvantages. Like any form of treatment, it can also lead to side effects such as rashes, asthma, headaches, dizziness, agitation, dry mouth, seizures, fatigue, tachycardia, nausea, vomiting, and diarrhea [103]. These side effects can vary in severity and frequency, and it's crucial for patients and healthcare providers to be aware of these potential drawbacks when considering herbal medicine as a treatment option [104]. It's also important to remember that herbal medicines can interact with other medications, potentially leading to adverse reactions [102].

While herbal medicine has made significant strides in treating diseases like Chagas disease in countries like Brazil, its effectiveness and mechanisms against Chagas disease are still being investigated [55]. The properties of herbal medicine, such as antipyretic, sedative, analgesic, anti-inflammatory, antioxidant, hepato-protective, chemo-preventive, and immune-mediated actions, are well-documented in the treatment of Chagas disease [55]. However, more research is needed to fully comprehend and utilize the potential of herbal medicine in the treatment of Chagas disease [55]. This includes identifying the active ingredients, understanding their mechanisms of action, and conducting rigorous clinical trials to establish their safety and efficacy [55]. With continued research and development, herbal medicine holds immense promise in combating Chagas disease and other health challenges [55].

The application of herbal medicine in managing Chagas disease is not a novel idea. In fact, for centuries, traditional healers across the globe have been employing herbs to combat this disease [97]. These age-old practices, deeply embedded in the culture and beliefs of the people, have been handed down through generations. The herbs used in these treatments are often readily available locally and are prepared in a variety of ways, including decoctions, infusions, and tinctures [55]. Some of the herbs commonly used to treat Chagas disease include *Lippia alba*, Asteracae, *Artemisia annua*, *Uncaria tomentosa*, and *Echinacea purpurea*, among others.

The scientific community has acknowledged the potential of these herbs in treating Chagas disease, and numerous studies have been conducted to investigate their effectiveness. These studies have yielded promising results, with some herbs demonstrating significant anti-parasitic activity against *Trypanosoma cruzi*. For instance, a study by Martínez-Peinado et al. (2021) [55] found that the extract of *Artemisia annua* effectively inhibited the growth of the parasite in vitro. Similarly, a study by Mintah et al. (2019) [3] found that the extract of *Uncaria tomentosa* exhibited a potent anti-parasitic effect against *Trypanosoma cruzi*.

Despite these encouraging results, the use of herbal medicine in the treatment of Chagas disease comes with its own set of challenges. One of the major challenges is the lack of standardization in the preparation and administration of these herbal remedies. This can lead to variations in the potency and effectiveness of the treatment, making it challenging to draw definitive conclusions about their efficacy [2]. Moreover, the safety of these herbal remedies is also a concern, as some herbs can have toxic effects when used in high doses or for extended periods [55].

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Another challenge is the lack of awareness and acceptance of herbal medicine in certain parts of the world. Despite the significant advancements made in the field of herbal medicine, it is still viewed with skepticism by some healthcare providers and patients [3]. This is often due to a lack of understanding about the science behind herbal medicine and a lack of trust in its efficacy. However, with ongoing research and education, it is hoped that this perception will change, and herbal medicine will be recognized as a viable treatment option for Chagas disease [10].

Herbal medicine holds considerable potential in the treatment of Chagas disease. With its rich array of bioactive compounds, it offers a promising alternative to conventional drugs. However, more research is needed to fully comprehend and utilize the potential of these natural remedies [7]. With continued research and development, it is hoped that herbal medicine will play a crucial role in the fight against Chagas disease and other health challenges. As the saying goes, "Nature is the best physician," and it is high time we tapped into the vast reservoir of healing potential that nature has to offer [10].

Mechanistic Strategy

Chagas disease, a significant health issue, currently has no specific antiviral medications for its treatment. This tropical parasitic disease, caused by the Trypanosoma cruzi, has been a major cause of illness and death, particularly in the Americas where it is endemic. The disease is named after Carlos Chagas, a Brazilian doctor who first identified the disease in 1909. Despite over a century of research, there are still no specific antiviral medications available for treating Chagas disease [105].

The number of Chagas disease cases has seen a substantial increase, from less than 0.5 million in 2010 to over 3.34 million in 2016 [98]. This increase can be attributed to several factors, including increased migration from endemic areas, improved diagnostic methods, and increased awareness of the disease. In India, the National Vector Borne Disease Control Programme (NVBDCP) reported 136,422 Chagas disease cases and 132 deaths in 2019 [106]. These numbers underscore the global impact of Chagas disease and the urgent need for effective treatment strategies.

Research has underscored the importance of supportive therapy in managing Chagas disease, including the use of various plants from different tribes and geographical regions [97]. These plants, often used in traditional medicine, have been found to possess antiparasitic properties that can aid in the treatment of Chagas disease [2]. Some of these plants include *Artemisia annua*, *Uncaria tomentosa*, and *Echinacea purpurea*, among others. These plants contain bioactive compounds that can inhibit the growth of *Trypanosoma cruzi*, thus aiding in the treatment of Chagas disease.

The disease, spread by the Triatominae, also known as kissing bugs, has been the subject of significant research on platforms like PubMed, Research Gate, and Google Scholar. These bugs, which are nocturnal and feed on the blood of mammals, including humans, are the primary vectors of *Trypanosoma cruzi* [10]. The bugs become infected with the parasite when they feed on an infected mammal. The parasite is then transmitted to humans when the bug bites them and defecates on the wound, allowing the parasite to enter the bloodstream [5].

The pathogenesis of Chagas disease involves numerous viral and host factors. These include the non-structural protein 1 (NS1) viral antigen, variations in the Chagas genome, subgenomic RNA, antibody-dependent enhancement (ADE), memory cross-reactive T cells, anti-Chagas NS1 antibodies, and autoimmune responses. These factors play a pivotal role in the disease progression and can influence the severity of the disease. Understanding these factors can aid in the development of targeted therapies for Chagas disease [107].

Herbal remedies are selected for their broad spectrum of beneficial properties, including antipyretic, sedative, analgesic, anti-inflammatory, antioxidant, hepaprotective, chemopreventive, and immune-mediated effects [6]. These properties can help mitigate the symptoms of Chagas disease and enhance the patients' quality of life. However, it's crucial to note that while these remedies can provide symptomatic relief, they do not cure the disease.

Acute kidney injury (AKI) is a common severe complication of Chagas that escalates infection-related morbidity and mortality [106]. AKI can occur due to the parasite's direct effect on the kidneys

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or due to the immune response triggered by the infection. Early detection and management of AKI can aid in improving the patients' prognosis.

The effectiveness of Western medications has been hindered by the involvement of numerous factors and the coexistence of risk factors in Chagas disease [106]. These factors include the genetic diversity of the parasite, the host's immune status, and the presence of co-infections. Moreover, the side effects and the cost of the medications can also restrict their use, particularly in low-resource settings.

The plant *Lippia alba* has been found to be effective in treating Chagas disease, a significant tropical viral infection, as determined by herbal medicine [97]. *Lippia alba*, also known as bushy matgrass, is a plant native to Central and South America. It has been used in traditional medicine for its antispasmodic, analgesic, and anti-inflammatory properties [55]. Recent studies have shown that the plant can also exhibit antiparasitic effects against *Trypanosoma cruzi*, thus underscoring its potential in the treatment of Chagas disease.

Given the disease's impact, especially in the most affected countries, the development of a safe, affordable, and effective Chagas vaccine is of paramount importance. A vaccine can offer long-term protection against the disease and can be a cost-effective strategy for disease control. However, the development of a Chagas vaccine has been challenging due to the parasite's complex life cycle and the diversity of its strains [6].

Chagas disease is a significant health concern that necessitates immediate attention. While there are currently no specific antiviral medications for the treatment of the disease, supportive therapy, including the use of herbal remedies, can provide symptomatic relief [2]. The development of a Chagas vaccine is of utmost importance and can be a game-changer in the fight against this disease. However, more research is needed to fully understand the disease's pathogenesis and to develop effective treatment strategies [3].

A total of 85 publications met the criteria for analysis (Figure 2). The significance of research into the effects of medicinal plants on Chagas Disease is underscored by their utility in managing disorders. A variety of medicinal herbs are employed to treat Chagas disease (Table 1). An interesting finding pertains to the country where the investigations were conducted. According to the Table, research on potential medicinal plants for treating Chagas disease was carried out in 15 countries: Saudi Arabia, Brazil, Australia, United States, Colombia, Bolivia, Andes, Mexico, Ghana, Spain, Heliyon, Portugal, Korea, and Uruguay. With 50.7% of the research conducted in Brazil, 9.24% in Colombia, 7.69% in Mexico, and the remaining 32.27% in the other 12 countries. In the 85 studies that met the inclusion criteria, as shown in the Table 1, *Lippia alba* and Asteracae are thought to be the most examined plants in this study. This characteristic may be linked to *Lippia alba*'s strong ability to combat Chagas disease.

The limitations of the current study must be considered when interpreting the results of this review. Due to methodological differences in the experimental process and study design used in the final selected publications, caution is advised when generalizing these findings. Furthermore, despite our efforts to find articles using the chosen keywords, not all of the papers considered for inclusion were found, including those that did not meet the requirements and those that we were unable to download from the databases of PubMed, Research Gate, and Google Scholar due to access restrictions. It is plausible to conclude that different tribes in various locations may use medicinal plant products to treat Chagas disease based on the study's findings. However, it is important to consider the limited number of publications that can be found in PubMed, Research Gate, and Google Scholar. These publications involve searches that evaluate the supportive therapy used to treat Chagas disease and reveal numerous plants from various tribes across different geographical areas that can be used to treat the infection.

Conclusion

In conclusion, the examination of natural products with the potential to address Chagas disease through an in-depth analysis unveils a promising frontier in the quest for effective therapeutic strategies. The comprehensive exploration of various natural products, including compounds

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derived from plants, microbes, and marine organisms, sheds light on their diverse bioactive properties. These bioactive compounds exhibit considerable potential in combating the causative agent, *Trypanosoma cruzi*, and may offer novel approaches to Chagas disease treatment.

While the research landscape is promising, it is essential to acknowledge the existing limitations, including the need for more rigorous clinical trials, standardization of methodologies, and a deeper exploration of underlying mechanisms. Future studies should focus on bridging these knowledge gaps, emphasizing translational research to facilitate the integration of natural products into clinical practice.

In the pursuit of advancing Chagas disease treatment, the in-depth analysis of natural products serves as a catalyst for continued research and innovation. This exploration not only enriches our understanding of the potential therapeutic agents but also underscores the importance of diversified approaches in combating neglected tropical diseases. As we navigate this intricate landscape, the hope is that the insights gleaned from this analysis will pave the way for the development of novel, accessible, and sustainable interventions for Chagas disease.

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