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Patologia: Doenças Parasitárias

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APRESENTAÇÃO

No volume II da coleção Patologia intitulado: Doenças Parasitárias, apresentamos em capítulos, diversos artigos de pesquisas realizadas em diferentes regiões. A temática inclui estudos sobre doenças tropicais, protozooses e parasitoses; dados epidemiológicos, diagnósticos e tratamentos, bem como temáticas correlacionadas e alguns acidentes por animais peçonhentos.

As doenças parasitárias decorrem da presença de macroparasitas (p. ex. helmintos) e/ou microparasitas (p. ex. protozoários), e envolvem em seu ciclo, hospedeiros, isto é, organismos vivos em que os parasitas se desenvolvem. De modo geral, podem ser transmitidas de diferentes formas como: água ou alimentos contaminados, picadas ou fezes de insetos ou outros animais, sexualmente, através de transfusão sanguínea e transplante de órgãos, de mãe para filho durante a gestação; sendo que cada parasitose tem suas características de contaminação. Suas manifestações clínicas são variáveis dependendo do agente etiológico e o local onde se instala, e podem variar de leves e moderadas até graves.

Apesar dos avanços relacionados às medidas preventivas, controle e tratamento, e da diminuição significativa dos níveis de mortalidade; as doenças parasitárias ainda constituem um problema sério de Saúde Pública no Brasil. A incidência das parasitoses tem relação direta com as condições socioeconômicas, com hábitos alimentares e de higiene, crescimento populacional, com saneamento básico, aspectos climáticos, educação, entre outros. No intuito de aprofundar o conhecimento acerca das parasitoses, este volume traz informações de estudos regionais sobre as doenças parasitárias mais conhecidas.

A obra é fruto do esforço e dedicação das pesquisas dos autores e colaboradores de cada capítulo e da Atena Editora em elaborar este projeto de disseminação de conhecimento e da pesquisa brasileira. Espero que este livro possa somar conhecimentos e permitir uma visão critica e contextualizada; além de inspirar os leitores a contribuírem com pesquisas para a promoção de saúde e bem estar social.

Yvanna Carla de Souza Salgado

SUMÁRIO

CAPÍTULO 7

ANTITRYPANOSOMAL ETHNOPHARMACOLOGY IN THE BRAZILIAN AMAZON

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ABSTRACT: In the search for new alternatives for the treatment of diseases caused by protozoa, studies have directed efforts in research on natural compounds extracted from plants that are effective against them and that have reduced toxicity to human hosts. Among neglected diseases, Chagas disease is one that urgently needs new treatment alternatives, since it has been discovered more than 100 years ago and, up to the present time, there is still no efficient treatment. As a result, the present study aimed to perform a bibliographic review of the Antitrypanosomal Ethnopharmacology in the Brazilian Amazon. Up to the present moment, 62 species of plants of the Brazilian Amazon, distributed in 25 botanical families, have been found to have potential for the production of anti-*Trypanosoma cruzi* drugs. This potential is still underestimated, since approximately 5% of the vegetables in the Amazon region have been studied in relation to pharmacological characteristics. And this area is promising mainly for the production of drugs in the treatment of neglected diseases, which is a reality in the region. However, in order to advance these researches, it is necessary, besides financial support, the interaction between different laboratories and research groups, thus forming teams with professionals in different areas, which may enhance the level of research in the region and maximize the probability of discovery of new anti-*Trypanosoma cruzi* potential drugs.
KEYWORDS: Antitrypanosomal, Chagas disease and Ethnopharmacology.

RESUMO: Na busca por novas alternativas para o tratamento de doenças causadas por protozoários, estudos têm direcionado esforços em pesquisas sobre compostos naturais extraídos de plantas que são eficazes contra eles e que têm toxicidade reduzida para hospedeiros humanos. Dentre as doenças negligenciadas, a doença de Chagas é uma das que necessitam urgentemente de novas alternativas de tratamento, uma vez que foi descoberta há mais de 100 anos e, até o momento, ainda não há tratamento eficaz. Como resultado, o presente

estudo objetivou realizar a revisão bibliográfica da Etnofarmacologia Antitripanossomal na Amazônia brasileira. Até o presente momento, 62 espécies de plantas da Amazônia brasileira, distribuídas em 25 famílias botânicas, apresentam potencial para a produção de drogas anti-Trypanosoma cruzi. Esse potencial ainda é subestimado, uma vez que aproximadamente 5% dos vegetais da região amazônica foram estudados em relação às características farmacológicas. E essa área é promissora principalmente para a produção de medicamentos no tratamento de doenças negligenciadas, o que é realidade na região. No entanto, para avançar nessas pesquisas, é necessário, além do apoio financeiro, a interação entre diferentes laboratórios e grupos de pesquisa, formando equipes com profissionais de diferentes áreas, o que pode potencializar o nível de pesquisa na região e maximizar a probabilidade de descoberta de novas drogas potenciais anti-Trypanosoma cruzi.
PALAVRAS-CHAVE: Antitrypanosomal, doença de Chagas e Etnofarmacologia

1 I INTRODUCTION

1.1 Brief History

Triatomines are insects belonging to the family Reduviidae and subfamily Triatominae, being popularly known in Brazil by barbers. There are currently 153 species in the world, distributed in 18 genera (OLIVEIRA; ALEVI, 2007), according to Table 1.

These insects are widely distributed in the Americas, mainly found from the south of the United States to the south of Argentina, being of great importance, since they can transmit the etiological agent *Trypanosoma cruzi*, causer of American Trypanosomiasis, also denominated Chagas disease (CD) (BEZERRA; MENEGUETTI; CAMARGO, 2012).

Although the description of the first species (*Cimex rubrofasciatus*, now *Triatoma* rubrofasciata De Geer, 1773) occurred at the end of the eighteenth century, the contact of this insect with man is quite anterior (BEZERRA; MENEGUETTI; CAMARGO, 2012). The first reported news about the appearance and habits of triatomines occurred in 1590 and was made by Father Reginaldo de Lizárraga, while on an inspection trip to convents in Peru and Chile (BEZERRA; MENEGUETTI; CAMARGO, 2012). It is believed that, by virtue of some records, Charles Darwin also observed these insects on his voyage to South America aboard H.M.S. Beagle, in 1835 (BEZERRA; MENEGUETTI; CAMARGO, 2012).

Chagas disease - or American Trypanosomiasis - was discovered in 1908 by the Brazilian physician Carlos Chagas. He had to diagnose and study clinically the first human case of trypanosomiasis in a child, in 1909 (BEZERRA; MENEGUETTI; CAMARGO, 2012; JUBERG et al., 2004). With its discovery, Carlos Chagas honored the medical epidemiologist Oswaldo Cruz with his name on the causative agent *T. cruzi* (BEZERRA; MENEGUETTI; CAMARGO, 2012; NETO; PASTERNAK, 2009). To

date, Carlos Chagas is the only researcher to describe the etiologic agent, vector, host and disease, with Chagas disease being the only example of the history in which the causal agent was discovered before the disease itself (BEZERRA; MENEGUETTI; CAMARGO, 2012; TARTAROTTI, 2004).

Tribe	Genus	Species (n)
Alberproseniini	*Alberprosenia*	2
Bolboderini	*Belminus*	8
	Bolbodera	1
	Microtriatoma	2
	Parabelminus	2
Cavernicolini	*Cavernicola*	2
Rhodniini	*Psammolestes*	3
	Rhodnius	21
Triatomini	*Dipetalogaster*	1
	Eratyrus 2	2
	Hermanlentia 1	1
	Linshcosteus 6	6
	Meccus 6	6
	Mepraia 3	3
	Nesotriatoma 3	3
	Panstrongylus 15	15
	Paratriatoma 1	1
	Triatoma 74	74
Total		**153**

Table 1. Number of species in the subfamily Triatominae (OLIVEIRA; ALEVI, 2007).

These insects are widely distributed in the Americas, mainly found from the south of the United States to the south of Argentina, being of great importance, since they can transmit the etiological agent *Trypanosoma cruzi*, causer of American Trypanosomiasis, also denominated Chagas disease (BEZERRA; MENEGUETTI; CAMARGO, 2012).

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1.1 Epidemiology

Considered endemic in South and Central America, Chagas disease has also been spread to other parts of the world as a result of immigration, being more and more frequent the registries of the disease in the United States, in European countries, Australia and Japan (SCHMUNIS; YADON, 2010).

Worldwide, more than 14 million people are infected by the parasite that causes Chagas disease (BRASIL, 2008). It is estimated that around 100 million people are still at risk of contracting this disease (OYAFUSO et al., 2008). The annual incidence is 200,000 new cases registered in several countries, it is estimated that there are more than 300,000 individuals infected in the United States, 5,500 in Canada, 80,000 in Europe and the Western Pacific region, 3,000 in Japan and 1,500 in Australia (COURA; VIÑAS, 2010).

In Latin America, the disease affects about eight million people (RASSI- JR; RASSI; MARIN NETO, 2010), being among the four main endemics, being one of its major health problems (ARGOLO et al., 2008). It mainly affects the populations of the poor countries of the American continent (TARTAROTTI et al., 2004; CARNEIRO-FILHO; LIMA, 2008). Endemic countries include those in South America such as Colombia, Venezuela, Ecuador, Peru, Brazil, Bolivia, Chile, Uruguay, Argentina and, in Central America, Mexico (TARTAROTTI et al., 2004).

Until the early 90's, Chagas disease was classified by the World Bank as the most serious of parasitic diseases in Latin America, with a socio-economic impact (measured as DALY - Disability-Adjusted Life Years) considerably higher than the combined effects of all the other parasitic infections (DIAS; PRATA; SCHOFIELD, 2002).

In Brazil, it is estimates that there are approximately 1.9 million people infected by *T. cruzi*. Although Brazil has been declared free of vector transmission of Chagas disease by *T. infestans*, acute cases have still been recorded due to transmission by wild triatomine species, mainly in the Amazon region.

Currently, new cases and outbreaks of acute Chagas disease (ACD) have been most recorded in the Legal Amazon region, where Chagas disease started to cause problems as a human disease in the Amazon, starting in 1969 and with greater emphasis from 1996 (PINTO et al., 2007).

From June 2006 to June 2007, 116 people were infected with the disease in the State of Pará after ingesting typical juices from the region (mainly açaí and bacaba) crushed with the barber (REIS, 2007). According to the Evandro Chagas Institute, from 1968 to 2005, on average, 12 cases per year were recorded in the Amazonian region orally, that is, there was an increase of 867% (REIS, 2007).

Between 2007 and 2011, there were 849 cases of ACD in Brazil, most of them by oral transmission (70%). Of these cases, 611 (72%) were diagnosed in the State of Pará (BRASIL, 2012). The Ministry of Health points out at least three reasons for this situation: the underreporting of cases until then, deforestation and burning in the Amazon and lack of care with hygiene in the artisanal processing of the fruit (BRASIL, 2005).

The same was observed in the State of Acre, a Brazilian State where the first autochthonous case was recorded in the 80's (BARATA et al., 1988). Recently, in the year 2016, two outbreaks caught the attention: one in the region of Alto Juruá, where 9 cases were registered, three of which evolved to death (BARBOSA, 2016), and another in the municipality of Feijó, with confirmation of 17 cases (Nascimento, 2016a), which influenced an increase of more than 216% in cases of Chagas disease in the State of Acre (NASCIMENTO, 2016).

1.2 Treatment

In the treatment of human infection, hundreds of drugs were tested against CD. The first compounds developed experimentally for the specific treatment of CD, after its discovery in 1909, were atoxyl (arsenic), tincture of fuchsin, emetic tartar (pentavalent antimonial) and mercury chloride. All of these compounds proved to be ineffective in the proposed treatment (BEZERRA; MENEGUETTI; CAMARGO, 2012; COURA; CASTRO, 2002).

In 1636, a quinoline derivative with mildly parasiticidal activity was first used in the treatment of the acute form of CD (BEZERRA; MENEGUETTI; CAMARGO, 2012; MAZZA; CÁSSIO; ZUCARDI, 1937; OLIVEIRA et al., 2008). In 1968, a meticulous evaluation of the drugs available for *T.cruzi* under *in vitro* and *in vivo* conditions was performed. Based on the results obtained, 27 compounds and more than 30 antibiotics were considered inactive and others presented suppressive effects of parasitemia, but no curative effects were observed: bisquinaldine, aminoquinolines (pentaquine, isopentaquine and primaquine), trivalent arsenic, aminoglycosides, nitrofurans and the antibiotics (BEZERRA; MENEGUETTI; CAMARGO, 2012; BRENER, 1968).

In the late 60's and early 70's, encouraging events occurred for the treatment of CD, resulting in drugs such as nifurtimox and benzonidazole (Figure 3), with nifurtimox (5-nitrofuran) being introduced in therapy in 1967 (MAZZA; CÁSSIO; ZUCARDI, 1937), and benzonidazole (2-nitroimidazole) in 1972(BEZERRA; MENEGUETTI; CAMARGO, 2012; MAZZA;CÁSSIO; ZUCARDI, 1937; CROFT; BARRET; URBINA, 2005).

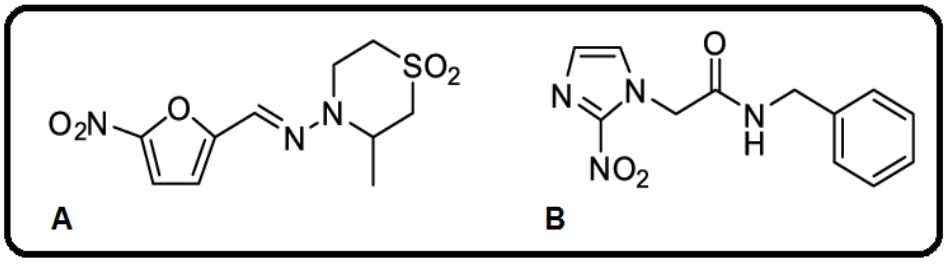

Figure 3. Chemical structure of the: a) Nifurtimox, b) Benzonidazole

Nifurtimox was withdrawn from the market because of the various side effects suffered by patients, and since the 80's, nifurtimox has been discontinued, first in Brazil and then in other South American countries (BEZERRA; MENEGUETTI; CAMARGO, 2012; MAZZA; CÁSSIO; ZUCARDI, 1937; RASSI et al., 2002). On the other hand, benzonidazole, a little more effective, although it presents moderate toxicity, it manages to decrease the parasitic rate in the blood and the tissues, if administered in the right dose and during the period of two months in the acute phase. However, no drug has demonstrated curative ability (BEZERRA; MENEGUETTI; CAMARGO, 2012; RASSI et al., 1999).

Some drug combinations are also cited (Table 2). These drug interactions and treatment times should be adapted according to the observation of side effects.

Drugs and Doses	Duration
Nifurtimox 8mg / kg / day + Benzonidazole 5mg / kg / day	60 days
Nifurtimox 8mg / kg / day + Allopurinol 8-10mg / kg / day	60 days
Benzonidazole 5mg / kg / day + Allopurinol 8-10mg / kg / day	60 days
Nifurtimox 8mg / kg / day + Ketoconazole 5-6mg / kg / day	60 days
Nifurtimox 8mg / kg / day + Fluconazole 5-6mg / kg / day	60 days
Nifurtimox 8mg / kg / day + Itraconazole 5-6mg / kg / day	60 days
Benzonidazole 5mg / kg / day + Ketoconazole 5-6mg / kg / day	60 days
Benzonidazole 5mg / kg / day + Fluconazole 5-6mg / kg / day	60 days
Benzonidazole 5mg / kg / day + Itraconazole 5-6mg / kg / day	60 days

Table 2. Combinations of drugs, used in the treatment of DC (BEZERRA; MENEGUETTI; CAMARGO, 2012; COURA, 2009).

Other double or triple associations can be tested, between drugs with different mechanisms of action. This proposal does not preclude investigations of new drugs to eliminate the etiological agent, but until the drug ideal for the specific treatment of CD is discovered, new strategies need to be developed to achieve greater efficacy with the old drugs, using combinatorial treatments and developing courses of rational experimentation for new drugs (BEZERRA; MENEGUETTI; CAMARGO, 2012; COURA, 2009).

To date, the two main drugs used in the treatment of CD are nifurtimox and

benzonidazole, even almost 50 years after its discovery. Some researchers have described that research on the control of transmission and management of (CD) infected patients is discouraged due to the lack of investments, because it is a neglected disease that has little potential for overall profit for pharmaceutical companies (MALAFAIA; RODRIGUES, 2010).

In her doctoral thesis, researcher Chung Man Chin, presents the efficiency that the chemical compound nitrofural demonstrates in exterminating the *T.cruzi*. "Nitrofural is used as a topical antimicrobial because of its high degree of toxicity, but it presents high activity against the parasite", says Chung. Thus, the proposal was to reduce this toxicity so that the compound could be used orally and for treatment during the chronic phase of the disease. For this, Chung modified the molecule of nitrofural, provoking a change that increases the selectivity for the parasite. Nitrofural has a high mutagenic action and low solubility, which causes it to be consumed in large quantities. This is the reason for the toxicity of this substance, which can cause hemolysis (breakdown of blood cells), much discomfort, nervous diseases, among other changes. "There are no drugs without adverse side effects, but the idea is to reduce them to the maximum", says Chung, who found that, among the synthesized derivatives, hydroxymethylnitrofural was the most active in tests performed on *in vitro* cells and the one that presented less toxicity (BEZERRA; MENEGUETTI; CAMARGO, 2012; BOSQUESI et al., 2008).

Other chemotherapeutic agents were tested as: TAK-187 and Ravuconazole, Allopurinol, Megazole and Naphthoimidazoles (OLIVEIRA et al., 2008), but none had significant results on its efficiency (BEZERRA; MENEGUETTI; CAMARGO, 2012). Posaconazole, an analogue of itraconazole, has been registered in the European Union, Australia and the United States as a systemic antifungal and is considered a strong candidate for new specific treatments of CD (BEZERRA; MENEGUETTI; CAMARGO, 2012; OLIVEIRA et al., 2008).

The effects of B and T lymphocytes (CD4 and CD8) were also investigated on benzonidazole and posaconazole. They showed that the survival rate of mice infected with *T.cruzi* and treated with said compounds was 100%, with about 87% of them being cured after treatment. However, the results indicated that when the infected mice had the presence of the T lymphocyte (CD4) in their immune system, the parasites reappeared after the drug effect, and the survival rate fell to 6%. The result of the treatment in the presence of the T lymphocyte (CD8) was considered intermediate, with survival rates between 81% and 86%, and cure between 31% and 66%. Yet, in the presence of B lymphocyte, the two drugs had different effects. Treatment with benzonidazole resulted in 67% survival rate, with cure rate of 22%. Posacononozole, however, had a more beneficial effect on these animals, accounting for 71% of cure and 100% of survival (BEZERRA; MENEGUETTI; CAMARGO, 2012; FERRAZ, 2009).

CD is a current, global and neglected problem. It does not interest the pharmaceutical industry because of the economic profile of the patients, who are usually economically disadvantaged people. The disease has also not been adequately assisted by

governments and is still poorly understood even by physicians, whose training has very few hours on the subject in some institutions (BEZERRA; MENEGUETTI; CAMARGO, 2012).

The CD is framed in a group of diseases where they are known as “Neglected Diseases”, that receive this name because these are diseases that affect thousands of people, in the great majority, with low income and in underdeveloped countries (BEZERRA; MENEGUETTI; CAMARGO, 2012). It is believed that the little investment in their treatment and prophylaxis is due to the level of the population living where these diseases normally occur (BEZERRA; MENEGUETTI; CAMARGO, 2012; DNDI, 2006).

Among the diseases that belong to this group, besides CD, we can mention malaria, leishmaniosis, filariasis and dengue. *Drugs for Neglected Diseases Initiative* reports that only 1% of the 1,393 new drugs registered between 1975 and 1999 were targeted at tropical diseases. These numbers reveal the existence of an excluding research policy, in which only 10% of the world health research expenditure is spent on diseases that represent 90% of the global burden (BEZERRA; MENEGUETTI; CAMARGO, 2012; SOBRINHO et al., 2007).

Besides, they often reside in places of difficult access, where they are helpless in relation to basic health, having to look for alternative treatments in plant biodiversity for their illness. However, about 99% of the plants of this region have not yet proven their pharmacological effect and their active principles have not been identified, which represents a major pharmacological and economic potential to be exploited (MENEGUETTI et al., 2014).

Different researchers have demonstrated the popular use of plants in the treatment of parasites such as malaria, leishmaniosis and Chagas disease. Many compounds isolated from plants such as chalcones, alkaloids, nalftoquinones, lignans, neolignans and terpenoids have already described their promising activity against protozoa (MENEGUETTI et al., 2015; RONDON et al., 2012).

In the search for new alternatives for the treatment of diseases caused by protozoa, studies have directed efforts in research on natural compounds extracted from plants that are effective against *them* and that have reduced toxicity to human hosts (MENEGUETTI et al., 2014; MENEGUETTI et al., 2015). As a result, the present study aimed to perform a bibliographic review of the Antitrypanosomal Ethnopharmacology in the Brazilian Amazon.

2 I METODS

The method used in the present study was a non-systematic review of the literature. Scientific articles, books and official documents of research centers are used, demonstrating the Brazilian Amazon the Antitrypanosomal Ethnopharmacology in the Brazilian Amazon.

3 I DISCUSSION AND RESULTS

3.1 Antitrypanosomal Ethnopharmacology

Medicinal plants have long been used in the treatment of parasitic diseases, and many studies corroborate the therapeutic importance attributed to products of plant origin, as well as describe the trypanosomicidal activity of several natural active principles. The administration of a natural drug, with low toxicity, would cause fewer side effects in the patient. Another advantage would be the lower cost for the population, especially if the drug came from an easily grown plant (BEZERRA; MENEGUETTI; CAMARGO, 2012; MARQUES, 2010).

Several plants in the Brazilian Amazon can be considered as candidates for the production of a drug against Chagas disease, since they have proven *in vitro* or *in vivo* activities against Chagas disease, leishmaniosis or malaria (BEZERRA; MENEGUETTI; CAMARGO, 2012; MENEGUETTI et al., 2014; MENEGUETTI et al., 2015; GUIMARÃES; FARIA, 2007), all diseases caused by protozoa, with emphasis on leishmaniasis and Chagas disease, which belong to the same family Trypanosomatidae.

62 species of plants of the Brazilian Amazon, distributed in 25 botanical families (Table 3), have been found to have potential for the production of anti-*Trypanosoma cruzi drugs* (BEZERRA; MENEGUETTI; CAMARGO, 2012; MENEGUETTI et al., 2014; MENEGUETTI et al., 2015; GUIMARÃES; FARIA, 2007).

FAMILY	SPECIE
Annonaceae	*Annona foetida; Annona spinescens; Guatteria foliosa; Himatanthus obovatus; Himatanthus sucuuba; Xylopia aromática.*
Apocynaceae	*Aspidosperma cylindrocarpon; Aspidosperma excelsum; Aspidosperma rigidum; Aspidosperma spruceanum; Aspidosperma parvifolium, Aspidosperma oblongum, Aspidosperma megalocarpon, Aspidosperma ulei, Aspidosperma desmanthum, Aspidosperma oblongum* and *Aspidosperma vargasii;*
Araliaceae	*Hydrocotyle bonariensis*
Aracea	*Montrichardia linifera*
Aristolochiaceae	*Aristolochia cymbifera*
Asteraceae	*Bidens pilosa,* Trixis spp and Lychnophora spp;
Bignoniaceae	*Anemopaegma arvense, Cybistax antisyphilitica* and *Anemopaegma arvense;*
Cecropiaceae	*Cecropia pachystachya*
Celastraceae	*Maytenus guyanensis;*
Clusiaceae	*Garcinia brasiliensis;*
Combretaceae	*Combretum leprosum*
Euphorbiaceae	*Croton cajucara, Croton pullei, Croton Lechleri* and *Pera benensis;*
Fabaceae	*Copaifera reticulata, Copaifera martii, Copaifera paupera, Copaifera officinalis and Copaifera multijuga*
Gentianaceae	*Tachia grandiflora*

Lacistemataceae	*Lacistema pubescens*
Lecythidaceae	*Gustavia elliptica*
Malpighiaceae	Banisteriopsis caapi
Meliaceae	*Guarea kunthiana*
Moraceae	*Pourouma guianensis*
Piperaceae	*Piper glabratum, Piper acutifolium, Piper aduncum , Piper carniconnectivum, Piper tuberculatum, Pothomorphe umbellata and Montrichardia linifera*
Rutaceae	*Esenbeckia febrífuga*, *Galipea spp and Psychotria viridis;*
Simaroubaceae	*Picrolemma sprucei, Quassia amara* and *Simaba orinocensis;*
Solanaceae	*Physalis angulate*
Salicaceae	*Casearia sylvestris*
Verbenaceae	*Lippia alba* and *Lantana cujabensis*

Table 3. Species and families of the plants of the Brazilian Amazon, have been found to have potential for the production of anti-Trypanosoma cruzi drugs

Several classes, such as quinones, flavonoids, alkaloids and terpenes are active against the *T. cruzi*. Among the quinoa, we can mention: Naftoquinone b-lapachone, present in several plant species of family Bignoniaceae, has activity against the amastigote, epimastigote and trypomastigote forms of the parasite. Its chemical derivative, 3-allyl-b-lapachone, is active against trypomastigote forms and has been suggested as an alternative drug for use in blood banks (BEZERRA; MENEGUETTI; CAMARGO, 2012; GUIMARÃES; FARIA, 2007).

Plumbagine, isolated from *Pera benensis*, was 100% active at the concentration of 250 µg / mL of contaminated blood. Another plant popularly known as boldo, has benzoquinone embelin and also some alkyl phenols, and the embryo has shown activity against *T. cruzi*, with 100% lysis of the protozoa, at a concentration of 100 µg / mL (GUIMARÃES; FARIA, 2007).

Among the flavonoids, the following are mentioned: 3-methoxyflavolone penduletin and flavanone sacuranetine, isolated from *Trixis spp*, eliminated 99 and 100%, respectively, of the infected blood parasite at a concentration of 500 µg / mL (RIBEIRO et al., 1997). In the stratum of *Lychnophora spp*, seven active substances were isolated against trypomastigote forms of *T. cruzi,* among them the flavonoids luteolin and vicenina-2, which demonstrated significant trypanosomicidal activity at the concentration of 500 µg/mL (GRAEL; ALBUQUERQUE; LOPES, 2005). *Lychnophora spp* extract provided 10 flavonoids*:* that were tested against *T. cruzi*, and the most active substance was quercetin-3-methyl ether, which did not cause lysis of blood cells and at the dose of 500 µg/mL has shown promise for use against *T. cruzi* in blood banks (TAKEARA et al., 2003).

Some alkaloids with trypanosomicidal activity are also cited as: The 2-n-propylquinoline, chimanin B and chimanin D, isolated from *Galipea spp*, presented

activities similar to those of the reference drugs nifurtimox and benznidazole, against five strains of epimastigote forms of *T. cruzi* (GUIMARÃES; FARIA, 2007).

Several terpenes are reported in studies of trypanosomicidal compounds, such as: Caurenoic acid isolated from *Mikania obtusata* (ALVES et al., 1995), *Xylopia frutescens* and from *Viguiera aspillioides* (TAKAHASHI et al., 1994), presented 100% activity against *T.cruzi*, at the concentration of 1000 µg / ml of contaminated blood (ALVES et al., 1995; TAKAHASHI et al., 1994). Other terpenes with action anti-*T.cruzi* are: xylopic acid, isolated from *Xylopia frutescens*, caurenol, isolated from *Viguiera aspillioides* and from *Xylopia frutescens* (TAKAHASHI et al., 1994), diterpenes 17-hydroxycauranol and trachylobanoic acid, isolated from *Viguiera aspillioides*, terpenoids isolated from *Mikania stipulacea* and *Mikania hoehnei* (NASCIMENTO et al., 2004).

Linalool, isolated from the leaves of the species *C. cajucara*, presents action against promastigote cells of the species *L. amazonensis* (ROSA et al., 2003) and against epimastigote and trypomastigote cells of *T. cruzi* (SANTORO et al., 2007). The same was observed with essential oils that contain this metabolite in its chemical composition (MENEGUETTI et al., 2015; SANTORO et al., 2007). One of the mechanisms of action of linalool is to stimulate the production of reactive oxygen species, such as nitric oxide (NO), which inhibits mitochondrial respiratory chain activity and decreases the levels of adenosine triphosphate (ATP) and glutathione in cells (RONDON et al., 2012). Linalool also has antibacterial action on cariogenic and periodontopathogenic bacteria (PARK et al., 2012), acting against the species *S. aureus, E. faecalis, E. coli, Klebsiella oxytoca, Proteus mirabilis, Salmonella typhi* and *P. aeruginosa* (MAZZANTI; BATTINELLI; SALVATORE, 1998). Study carried out with the bacteria *S. aureus, E. coli* and *S. typhimurium* describes other mechanisms of action of linalool that cause alteration of permeability and function of the plasma membrane, loss of intracellular matter and, consequently, cell death (MENEGUETTI et al., 2015).

Casear metabolites isolated from *C. sylvestris* have demonstrated a good action against *T. cruzi* and *Leishmania* spp (BOU et al., 2014), probably because they caused the rupture of the parasite's plasma membrane. This causes depletion of ionic gradients, efflux of nutrients and other cytoplasmic components, causing osmotic lysis and, consequently, cell death (MENEGUETTI et al., 2015; MARR; MCGWIRE; MACMASTER, 2012).

Fractions of *C. sylvestris* are also characterized by the presence of substances of interest, such as: coumarins, flavonoids, lignans and various diterpenes (YAMAGUSHI; GUSMAN; VESTENA, 2011). Presenting action against *Leishmania donovani* promastigotes, *T. cruzi* amastigotes, and antimalarial activity action (MESQUITA et al., 2007), besides acting against larvae of *Aedes aegypti* (RODRIGUES et al., 2006) and present antimicrobial action against fungi: *Aspergillus niger*, Saccharomyces cerevisiae, *Candida albicans*, *C. tropicalis* and bacteria: *Bacillus subtilis*, *B. cereus*, *Staphyloccoccus aureus*, *Enterococcus faecalis*, *Salmonella enteritidis* (MENEGUETTI et al., 2015; FERREIRA et al., 2011).

Tingenone B isolated from *Maytenus guianensis*, showed antiparasitic activity against *T. cruzi* (IC <0.25 µg / mL), *Trypanosoma brucei* (IC <0.25 µg / mL) and *L. infantum* <0.51 µg / mL) (MENEGUETTI et al., 2016). Other compounds with the same skeleton showed great potential for the production of potent drugs against leishmaniasis and Chagas disease (BRASIL, 2005). Previous studies have shown that triterpenoids stimulate granulocytosis and phagocytosis, thus helping to combat infection, causing cytoplasmic extravasation, corpuscle formation and mitochondrial swelling. Another possible explanation for the anti-parasitic activities of these terpenoids is their activation of programmed cell death within the parasites50 and interference with the parasite cell differentiation process in the host. This is an extremely complex process involving fine regulation of gene expression (MENEGUETTI et al., 2016; DUSZENKO et al., 2011).

Gross extracts of Brazilian plant species, especially the family *Lauraceae,* have already shown, in *in vitro* trials, that may be useful in combating *T.cruzi*, whose growth has been inhibited by up to 100%. Synthetic substances, such as aromatic diamidines, have also been tested against parasite, showing high activity and selectivity (WU et al., 2012).

In a recent study, researchers tested *in vitro* the effect of crude extracts of 92 Brazilian plant species against the parasite *T. cruzi*, which causes CD. Of the extracts tested, 11 of them presented satisfactory results, seven of which inhibited the growth of the parasite between 50% and 90% and four of them reached an inhibition of 100% (MARQUES, 2010).

Several plants are cited for presenting anti-*T. cruzi* action, and among them we can mention: *Camellia sinensis* (PAVETO et al., 2004), *Baccharis trimera, Cymbopogon citratus, Matricaria chamomilla* Asteraceae*, Mikania glomerata* Asteraceae*, Ocimum gratissimum, Piper regnellii, Prunus domestica, Psidium guajava, Sambucus canadensis, Stryphnodendron adstringens, Tanacetum parthenium,* and *Tanacetum vulgare* both have a significant effect against the parasite, with the percentage of inhibition of growth between 49.5 and 99%. The extracts showed no cytotoxic effect on sheep red blood cells. These medicinal plants may be alternative sources of new compounds clinically active against *T. cruzi* (BEZERRA; MENEGUETTI; CAMARGO, 2012).

In the Amazon region, we can also mention the *Banisteriopsis caapi* and *Psychotria viridis* that has anti-trypanosomal action against the *Trypanosoma lewisii* and *T. cruzi.* These plants are used in the preparation of a tea known as (Ayahuasca) which is used in religious rituals, and it is believed that it is due to the use of this tea that indigenous people are not infected by *T. cruzi* and *Leishmania sp* (MENEGUETTI; MENEGUETTI, 2014).

4 I FINAL CONSIDERATIONS

Up to the present moment, 62 species of plants of the Brazilian Amazon, distributed in 25 botanical families, have been found to have potential for the production of anti-*T. cruzi* drugs. This potential is still underestimated, since approximately 5% of the vegetables in the Amazon region have been studied in relation to pharmacological characteristics. And this area is promising mainly for the production of drugs in the treatment of neglected diseases, which is a reality in the region. However, in order to advance these researches, it is necessary, besides financial support, the interaction between different laboratories and research groups, thus forming teams with professionals in different areas, which may enhance the level of research in the region and maximize the probability of discovery of new anti-*Trypanosoma cruzi* potential drugs.

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