

Clinical and symptomatological characterization regarding Chagas disease caused by the *Trypanosoma cruzi* parasite

Caracterização clínica e sintomatológica referente à doença de Chagas provocada pelo parasita *Trypanosoma cruzi*

Caracterización clínica y sintomática de la enfermedad de Chagas causada por el parásito *Trypanosoma cruzi*

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Abstract

Neglected diseases are a group of communicable diseases that mainly affect tropical regions of developing countries. Among this group of diseases is Chagas disease, which has been classified among the six most important parasitic diseases in the world, and it is estimated that more than one billion people are at risk in endemic countries. The objective of this study is to review the literature on the symptomatological and clinical characterization of Chagas disease caused by *Trypanosoma cruzi*. This is an integrative literature review study. For this, we used the following descriptors in the search: *Trypanosoma cruzi*, epidemiological profile, Chagas disease and clinical aspects (together and separately). In the selection criteria we opted for full articles, in the period 2013 - 2021 (last 9 years), in Portuguese and English. The searches were conducted in the following databases: Scientific Electronic Library Online (SciELO), Pubmed, Latin American and Caribbean Literature on Health Sciences (Lilacs), Google Scholar. The articles were selected first by title, then by abstract, and finally by complete reading. The literature shows that Chagas disease is caused by the protozoan *Trypanosoma cruzi*, characterized by the presence of a flagellum and kinetoplast. Some of its clinical manifestations include: fever, asthenia, adynamia, myalgia, arthralgia, headache, myocarditis, and hepatosplenomegaly. Therefore, it is important to know all the characteristics of this disease, since it can be considered a public health problem. It is suggested that new studies be carried out with different approaches, in order to elucidate even more specifically the dynamics surrounding this disease.

Keywords: *Trypanosoma cruzi*; Epidemiological profile; Chagas disease; Clinical aspects.

Resumo

As doenças negligenciadas são um conjunto de doenças transmissíveis, que afetam principalmente regiões tropicais de países em desenvolvimento. Dentre esse conjunto de doenças se destaca a doença de Chagas, que foi classificada entre as seis doenças parasitárias mais importantes do mundo, e estima-se que mais de um bilhão de pessoas estão em risco em países endêmicos. Neste sentido o objetivo desse estudo é de fazer uma revisão de literatura sobre a caracterização sintomatológica e clínica da doença de Chagas causadas pelo *Trypanosoma cruzi*. Trata-se de um estudo de revisão da literatura do tipo integrativa. Para tanto, utilizamos na busca os descritores: *Trypanosoma cruzi*, perfil epidemiológico, doença de Chagas e aspectos clínicos (juntos e separados). No critério de seleção optamos por artigos completos, no período de: 2013 – 2021 (últimos 9 anos), nos idiomas: português e inglês. As buscas foram realizadas nos bancos de dados: *Scientific Electronic Library Online* (SciELO), Pubmed, *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (Lilacs) Google acadêmico. Os artigos foram selecionados primeiramente por título, posteriormente por resumo, e por fim, por leitura completa. A literatura evidencia que a doença de Chagas é causada pelo protozoário *Trypanosoma cruzi*, caracterizado pela presença de um flagelo e do cinetoplasto. Algumas de suas manifestações clínicas incluem: febre, astenia, adinamia, mialgia, artralgia, dor de cabeça, miocardite e hepatoesplenomegalia. Portanto, é importante que se conheça todas as características desta doença, já que ela pode ser considerada um problema de saúde pública. Sugere-se que novos estudos sejam realizados com abordagens diferentes, para que seja elucidado de forma ainda mais específica a dinâmica envolta dessa doença.

Palavras-chave: *Trypanosoma cruzi*; Perfil epidemiológico; Doença de chagas; Aspectos clínicos.

Resumen

Las enfermedades olvidadas son un grupo de enfermedades transmisibles que afectan principalmente a las regiones tropicales de los países en desarrollo. Entre este conjunto de enfermedades se encuentra la enfermedad de Chagas, que ha sido clasificada entre las seis enfermedades parasitarias más importantes del mundo, y se estima que más de mil millones de personas están en riesgo en los países endémicos. En este sentido, el objetivo de este estudio es realizar una revisión bibliográfica sobre la caracterización sintomatológica y clínica de la enfermedad de Chagas causada por *Trypanosoma cruzi*. Se trata de un estudio de revisión bibliográfica integradora. Para ello, se utilizaron los siguientes descriptores en la búsqueda: *Trypanosoma cruzi*, perfil epidemiológico, enfermedad de Chagas y aspectos clínicos (juntos y por separado). En los criterios de selección se optó por artículos completos, en el período 2013 - 2021 (últimos 9 años), en portugués e inglés. Las búsquedas se realizaron en las siguientes bases de datos: Scientific Electronic Library Online (SciELO), Pubmed, Latin American and Caribbean Literature on Health Sciences (Lilacs), Google Scholar. Los artículos se seleccionaron primero por el título, luego por el resumen y finalmente por la lectura completa. La literatura muestra que la enfermedad de Chagas está causada por el protozoo *Trypanosoma cruzi*, caracterizado por la presencia de un flagelo y un cinetoplasto. Algunas de sus manifestaciones clínicas son: fiebre, astenia, adinamia, mialgia, artralgia, cefalea, miocarditis y hepatoesplenomegalia. Por ello, es importante conocer todas las características de esta enfermedad, ya que puede considerarse un problema de salud pública. Se sugiere que se realicen nuevos estudios con diferentes enfoques, con el fin de dilucidar aún más específicamente la dinámica que rodea a esta enfermedad.

Palabras clave: *Trypanosoma cruzi*; Perfil epidemiológico; Enfermedad de chagas; Aspectos clínicos.

1. Introduction

Neglected diseases are a group of communicable diseases that mainly affect tropical regions in developing countries. Populations living in poverty, without adequate sanitation, and in contact with infectious vectors are the most affected by these diseases. They are called "neglected" because there is little interest in the development of new treatments by the pharmaceutical industry. This fact can be attributed to the low financial return for these industries. Among this set of diseases is Chagas disease, which has been classified among the six most important parasitic diseases in the world, and it is estimated that more than one billion people are at risk in endemic countries (Who, 2017).

American trypanosomiasis or Chagas disease is an infectious and parasitic disease, which presents as the causative agent the *T. cruzi*, which parasitizes mammals and has as hosts the invertebrates, there are several forms of the vector of hematophagous species of the *Reduviidae* family known as barbers and different forms of the vector presented in the cycle but not all are infectious to man (Sánchez-Valdéz et al., 2018).

Triatomines are the parasites responsible for the vectorial transmission of Chagas disease, they are hematophagous insects that belong to the genera *Rhodnius*, *Panstrongylus* and *Triatoma* that have in their organism the *T. cruzi* that is the causative agent of the disease (Jansen, 2018; Dumonteil et al., 2018).

The first observation made by Carlos Chagas and his description of *T. cruzi*, were performed by fixing the parasite with Giemsa dye a method that is still used today, with the optical microscopy could be seen the identification of the parasite with the general form of its cell the nucleus, kinetoplast, mitochondrial DNA condensed, with its epimastigotes, tripomastigas and amastigotes forms, in this technique the visualization of the parasites are more evidenced different from the examination of fresh blood that are not well identified all these structures of the parasite (Silva et al., 2019).

The initial infection or reinfection occurs through the inoculation of the metacyclic trypomastigotes forms of *T. cruzi* in the body of the reservoir host when the triatomines are infected, after some time of inoculation the infecting forms of the parasite are released in the urine or feces of the insect, soon after the transmission cycles occur where the parasite will pass its infecting forms to man and thus complete its evolutionary cycle (Cordeiro, 2020).

There are several forms of transmission described among which one of the most worrisome today is oral transmission by ingestion of infective forms of the parasite, in the vector form prevention programs have been carried out on elimination of the barbeiro (Santana et al., 2019).

Despite the lack of systematic data regarding the prevalence of the disease, in recent studies the prevalence estimate

ranged from 1.0 to 2.4% of the population, which is equivalent to 1.9 to 4.6 million people infected with *T. cruzi* in the country. This is reflected in the high mortality from the disease in Brazil, as it is one of the four leading causes of death from infectious and parasitic diseases (Vargas et al., 2018).

The treatment of Chagas disease consists of therapies that have several adverse effects and also long treatment periods leading about 15-20% of patients to drop out of treatment (Muller, 2018). Thus, the research and development of new drugs for neglected diseases are necessary.

Thus, the objective of this study is to conduct a literature review on the clinical and symptomatological characterization of Chagas disease caused by the *Trypanosoma cruzi* parasite.

2. Methodology

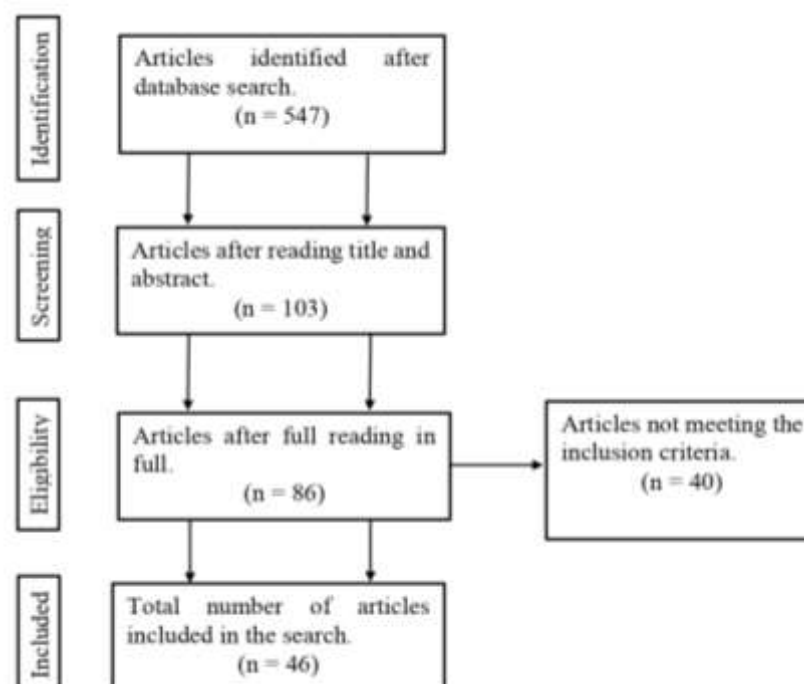
2.1 Type of study

To meet the objectives that were previously proposed, this work is an integrative literature review study. For Sousa (2017) this research model can be considered as a mechanism of investigation that adheres to investigative questions, careful evaluation, and the synthesis of the evidence that is available on the given theme that is under investigation.

2.2 Search procedure

The search for primary studies was performed according to the criteria and manuals of each database. Controlled descriptors were used: *Trypanosoma cruzi*, neglected diseases, parasitoses (jointly and separately), combined with Boolean operators (AND and OR). The descriptors, as well as the articles selected to compose this study were searched between January and March 2021, in the following databases: *Scientific Electronic Library Online* (SciELO), PubMed, *Latin American and Caribbean Literature on Health Sciences* (LILACS), and Google Scholar. The articles were selected first by title, then by abstract, and finally by complete reading.

Figure 1. Flowchart of the article search and screening process.



Source: Authors (2021).

2.3 Guiding Question

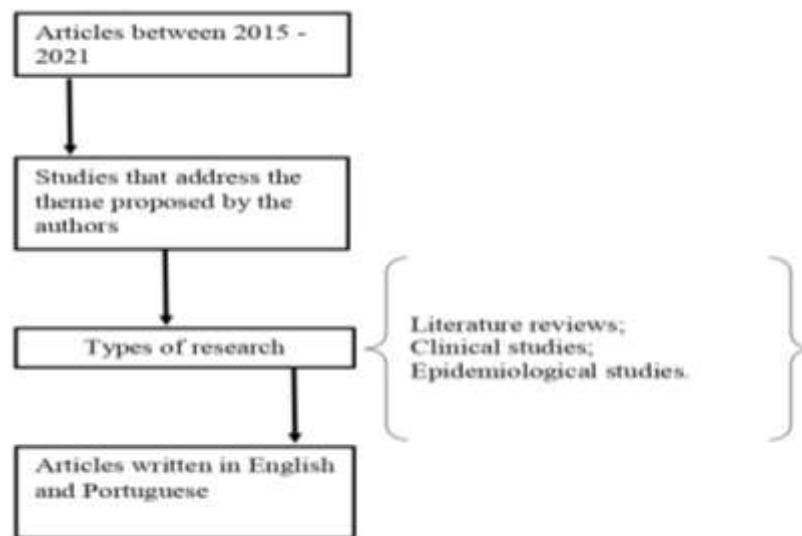
To guide the integrative review, the following guiding question was formulated: "What is the scientific evidence in the literature on the clinical aspects and symptomatology of patients affected by Chagas disease?"

2.4 Inclusion and exclusion criteria

2.4.1 Inclusion Criteria

The inclusion criteria proposed for this research are shown below, see figure 2.

Figure 2. Inclusion criteria used in the survey.

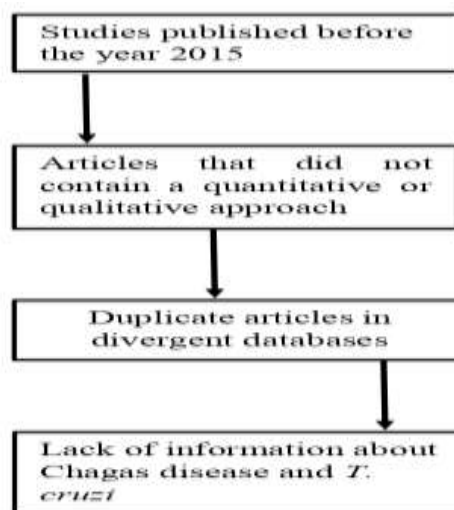


Source: Authors (2021).

2.4.2 Exclusion Criteria

The exclusion criteria proposed for this research are shown below, see figure 3.

Figure 3. Exclusion criteria used in the survey.



Source: Authors (2021).

2.5 Data Overview

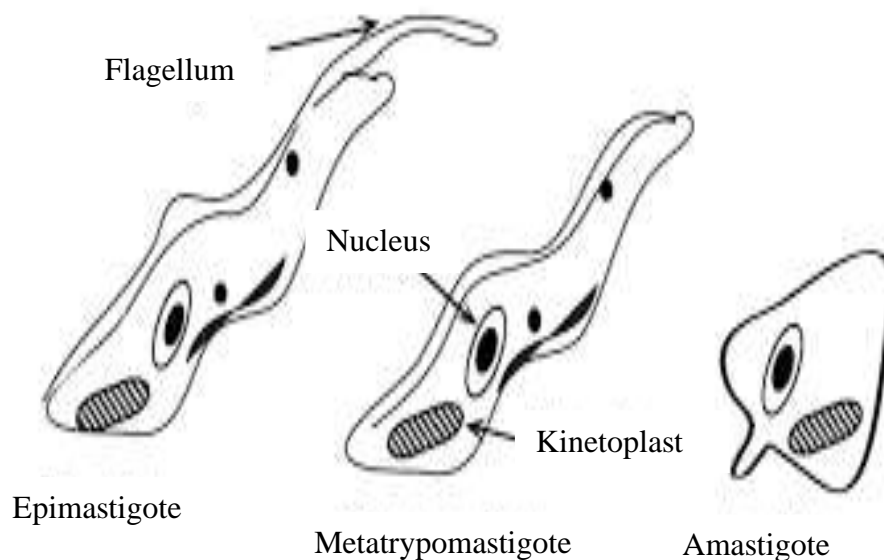
Given the established criteria, 27 scientific articles were selected to compose the theoretical foundation of this work. For the results and discussion of this research, the articles were explained about Chagas disease and *T. cruzi* regarding its (i) etiology; (ii) epidemiology; (iii) symptomatology and clinical aspects; (iv) diagnosis and treatment.

3. Results and Discussion

3.1 Etiology

The disease is caused by the protozoan *Trypanosoma cruzi*, characterized by the presence of a flagellum and kinetoplast. Its evolutionary forms are amastigotes, trypomastigotes and epimastigotes. For example, in the blood of vertebrates, *T. cruzi* presents itself as a trypomastigote, which is extremely mobile, and in the tissues as amastigotes. In the digestive tract of the vectors, the parasite is transformed, giving rise to the infective forms present in the insect feces. From this, it is possible to understand the transmission of CD and prevent the disease (Fidalgo et al., 2018; Zingales, 2018; Correa et al., 2021).

Figure 4. Evolutionary forms of *Trypanosoma cruzi*.



Source: Fiocruz.

3.2 Epidemiology

There are about 6 to 7 million people in the world with the disease, mainly distributed among the 21 Latin American countries. Brazil contributes with more than 1 million of these cases (WHO, 2015). Regarding the epidemiological scenario in Brazil, according to data from the Ministry of Health (Brazil, 2018), in the period from 2007 to 2016, cases of acute Chagas disease were confirmed in most states, with an annual average of 200 cases. About 95% of these cases were registered in the North region, mainly in Pará where 85% of these cases are. Regarding the main probable forms of transmission in the country, most (69%) were attributed to oral transmission (Boletim epidemiológico, 2015).

In a recent study, Souza et al., (2020) pointed out that the North, Midwest and the mid-north subregion of the Northeast of Brazil have a high incidence of infectious-parasitic diseases. Despite the reduction in the average indicators of poverty, the concentration of these diseases in these territories is linked to the socioeconomic inequality still present in the national scenario, which, in turn, has contributed to the illness of vulnerable groups affected by the historical structural

inequity. They also state that the presence of these pathologies ends up serving as an indicator of regional development, and can thus serve - as - a - guideline - for the construction of more inclusive public policies that promote improved health care and living conditions for vulnerable populations (Costa et al., 2018; Souza et al., 2020).

3.3 Symptomatology and clinical aspects

In the acute phase of Chagas disease, the patient may have few or no symptoms of the disease. Once these symptoms are ignored and the disease goes untreated, it can progress to the chronic phase, affecting the heart and gastrointestinal system (Espinosa-Álvarez et al., 2018).

Table 1. Main clinical manifestations in patients affected by Chagas disease.

SYMPTOMS OF CHAGAS DISEASE	
Fever	Nausea and vomiting
Malaise	Diarrhea
Localized swelling at the site of the barber's bite	Inflammation and pain in the ganglia
Swelling in the eyes	Nodules scattered throughout the body
Pain in the body	Redness all over the body
Headache	Enlarged liver and spleen
Tiredness and prostration	Complications of chagas disease include digestive problems, meningitis, heart problems such as chagasic carditis, and chronic constipation

Source: Authors (2021).

The systemic manifestations that may occur include fever, asthenia, adynamia, myalgia, arthralgia, headache, myocarditis, and hepatosplenomegaly. Myocarditis can occur with or without manifestations of cardiac involvement, such as tachycardia, gallop rhythm, prolongation of the PR and/or QT interval, decreased QRS voltage, premature ventricular contractions, right bundle branch block, T-wave changes, pericarditis, cardiac tamponade, and heart failure (Benck et al., 2018; Brahmhatt, 2018).

3.4 Diagnosis and treatment

In the acute phase of Chagas disease, blood trypomastigotes can be detected only by direct parasitological methods, where the parasites are identified directly in the patient's blood test, by visualization of blood trypomastigotes. Indirect parasitological methods, such as xenodiagnosis and blood culture, can also be used. Serological tests are often used in the diagnosis of the chronic phase and are based on the detection of specific immunoglobulins against *T. cruzi* (Castro, 2018; Silva et al., 2020).

Table 2. Diagnostic methods for Chagas disease caused by *Trypanosoma cruzi*.

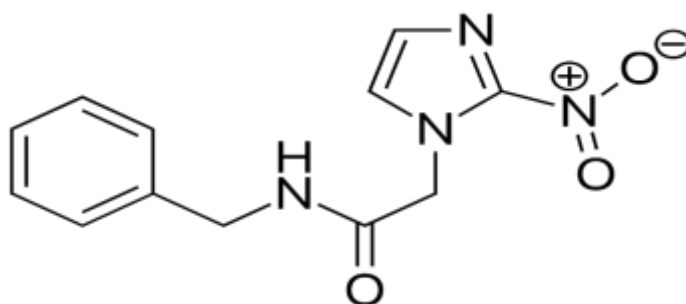
Main forms of diagnosis for Chagas disease	Methods
Direct parasitological examinations	Technique for diagnosis of the disease in the acute phase. Blood should be drawn for the processing of all the methodologies described below in order to expedite diagnosis.
Fresh Trypanosomatids research	It is used as the first alternative because it is easy and simple to perform. The ideal situation is to perform the collection with a febrile patient and within 30 days of the onset of symptoms.
Concentration Methods	They have higher sensitivity, and are recommended especially when the wet test is negative. Among the direct methods, they are indicated when the patient has had symptoms for more than 30 days.
Thick drop or smear stained slide	It has lower sensitivity than other direct methods, and is performed primarily in the Legal Amazon region, due to its use for malaria diagnosis, in cases of high parasitemia, such as transmission by transfusion, and in immunosuppressed patients
Indirect parasitological examinations	In the chronic phase of Chagas disease, the use of direct parasitological methods is unreliable, mainly due to the low parasitemia. Therefore, the use of indirect methods, such as xenodiagnosis and blood culture, is necessary to identify or not the presence of the parasites.
Serological examinations	For detection of IgG class anti- <i>T. cruzi</i> antibodies, two collections are necessary with a minimum interval of 21 days between one collection and the other. For confirmation it is preferably necessary paired execution, that is, negative serology in the first sample and positive in the second by any of the methods (Enzyme-linked immunosorbent assay - ELISA, Indirect Immunofluorescence - IFI or Indirect Hemagglutination - HAI) or the variation of at least two serological titles, by the IFI method.
Detection of IgM class anti- <i>T. cruzi</i> antibodies	A complex technique, with false-positive results in many febrile illnesses. To be performed, the patient must present clinical alterations compatible with ACD and a suggestive epidemiological history. It is more appropriate in the late acute phase when repeated direct investigation tests are negative.
Xenodiagnosis	This method aims to investigate the presence of parasites in the feces and/or intestinal contents of insect vectors kept in laboratories and fed with the blood of individuals to be tested. It is commonly used to check for chagasic infection in humans and animals. Four boxes containing ten triatomines each, closed on one side by a thin net, are placed on the ventral side of the patient's forearm for about thirty minutes. Before this examination is performed, the triatomines must be fasted for a period of two weeks. After feeding with blood from the patient, the insects should be kept at a temperature between 25°C and 30°C and relative humidity of approximately 85% in the absence of light. Fecal examination or examination of intestinal contents will be done after 30-60 days for patients in chronic phase and 10-30 days for patients in acute phase.
Hemoculture	There is a wide variety of culture media in which <i>T. cruzi</i> can multiply abundantly, such as blood agar-based diphasic media (NNN) and others. Liquid media such as LIT (<i>liver infusion tryotose</i>), BHI (<i>barin heart infusion</i>) and Waren's medium are also employed. This technique was not routinely used for several years, as it was a low-sensitivity method.
Indirect Immunofluorescence	This reaction has been widely used in the laboratory diagnosis of Chagas disease. The antigen is prepared with epimastigotes forms of <i>T. cruzi</i> , which are collected from the culture in LIT medium in the exponential phase of growth, washed and fixed in formalin solution, paraformaldehyde and/or lyophilized. Antibodies from patient serum are placed on a slide containing <i>T. cruzi</i> antigens. The anti- <i>T. cruzi</i> antibodies are revealed using fluorescein-conjugated human anti-immunoglobulin (Ig) antibodies and observed under a fluorescence microscope. The use of this method is mainly due to its advantages: relative ease of obtaining standardized reactions, high sensitivity, regularity of results, and the possibility of processing a large number of samples simultaneously.
Hemagglutination	It is a very simple, faster and more sensitive reaction than the complement fixation test for the detection of anti- <i>T. cruzi</i> antibodies in the serum of infected individuals. It is based on the agglutination of sheep red blood cells coated with <i>T. cruzi</i> cytoplasmic antigens in the presence of serum containing antibodies to this parasite. If <i>T. cruzi</i> antigen antibodies are present, they will form bonds between the RBCs, interacting with the antigens on their

	surface. Thus, visually there will be the formation of a mantle on the microtiter plates. Due to its low cost, clarity of results and simplicity of execution, it has been widely used in routine situations.
ELISA	This technique consists in detecting antibodies against the parasite by using a second antibody (human anti-immunoglobulin produced in laboratory animals), conjugated to enzymes, which, in the presence of specific substrates, generate colored products, whose quantification is done spectrophotometrically. This method offers high sensitivity, use of low quantities of serum, simultaneous processing of several samples and, finally, easy use in field work.
Polymerase Chain Reaction or PCR	This diagnostic method is based on the use of synthetic oligonucleotides that amplify pathogen-specific DNA sequences. However, the tests have not yet been made commercially available and are not used beyond the research environment. Besides the cost, the need to perform the test in high-tech laboratories with exclusive space for its execution can be cited as the main limiting factor regarding the use of PCR tests in outpatient or hospital settings, or even in the routine of blood banks, despite being a very important technique for the diagnosis of Chagas disease.
Western Blot	In this technique, the <i>T. cruzi</i> antigen is subjected to polyacrylamide gel electrophoresis for resolution of the proteins according to the molecular mass criteria. After transferring the gel fractionated material to nitrocellulose membranes, the antigen-antibody reaction procedure is similar to the ELISA method. The sera are placed on the nitrocellulose strips and in case of a positive reaction, characteristic bands will appear.

Source: adapted from Alves et al., (2018).

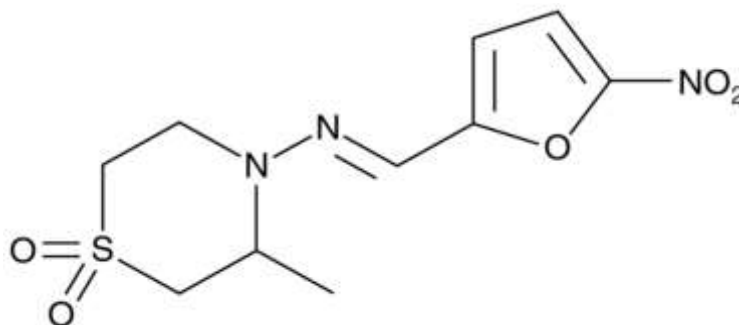
As for the treatment of Chagas disease, on the other hand, benznidazole (figure 5) and nifurtimox (figure 6) are currently recommended in both the chronic and acute phases of the disease, with lower cure rates during the chronic phase, acting on the parasite without reversing already established cardiac damage (Cardoso et al., 2018; Caldas, 2019; Jackson, 2020).

Figure 5. Chemical structure of benznidazole.



Source: Cayman Chemical.

Figure 6. Chemical structure of nifurtimox.



Source: Cayman Chemical.

Even with all the scientific relevance of these two compounds for the therapy of Chagas disease, studies show that there is a high toxicity content in the compositions of these substances, thus, new research points to the elucidation of new therapies based on drug synthesis, natural products or repositioning in order to obtain trypanocide drug candidates with fewer adverse effects (Bernstein et al., 2021).

4. Conclusion

Knowing the clinical importance of Chagas disease, taking into account its clinical and epidemiological aspects, it is important to note that studies involving this theme are always of paramount importance to the scientific community, since it is a theme with a broad spectrum of topics for research. New experiments and investigations are necessary to better elucidate the dynamics of infection by the parasite and also to identify other forms of treatment that are even more effective than the existing ones and with fewer toxicological effects.

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