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Revisión / Review

# Botanical compounds: A promising control strategy against Trypanosoma cruzi

[Compuestos botánicos: una estrategia de control prometedora contra *Trypanosoma cruzi*]

**Rao Zahid Abbas[1], Muhammad Abdullah Qureshi[2] & Zohaib Saeed[1]**

[1]Department of Parasitology, University of Agriculture, Faisalabad, 38040, Pakistan.
[2]Faculty of Veterinary Science, University of Agriculture, Faisalabad, 38040, Pakistan

**Reviewed by:**
Edmundo Venegas-Casanova
Universidad Nacional de Trujillo
Peru

Ahmed Salah Naser
University of Mosul
Iraq

**Correspondence**:
**Rao Zahid ABBAS**
raouaf@hotmail.com

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**Abstract:** Chagas disease, also known as American trypanosomiasis, is caused by *Trypanosoma cruzi*. It is a major health threat that affects 6-8 million people annually around the globe. Chagas disease is of zoonotic importance, infecting more than 100 species of sylvatic and domestic mammals. There are only two antibiotic drugs available for the treatment of this disease i.e., Benznidazole and Nifrutimox. Somehow, the parasite *Trypanosoma cruzi* has developed resistance against these available drugs. There is a need to develop new drugs for the prevention and treatment of Chagas disease. Research proves that botanical compounds can be effective against *T. cruzi*. Botanicals have shown potent results against bloodstream trypomastigotes, epimastigotes, amastigotes, and trypomastigotes stages of the *T. cruzi*. Botanical compounds of chalcones, phenolics, alkaloids, terpenoids, benzoic acids, and quinones have been proven to target *T. cruzi* directly. Direct mechanisms involve DNA damage, energy pathways disturbance, and disrupting cell membranes.

**Keywords:** *T. cruzi*; Chagas disease; Anti-Trypanosomal activity; Botanicals; Plant derivatives

**Resumen:** La enfermedad de Chagas, también conocida como tripanosomiasis americana, es causada por *Trypanosoma cruzi*. Es una amenaza importante para la salud que afecta a entre 6 y 8 millones de personas anualmente en todo el mundo. La enfermedad de Chagas tiene una importancia zoonótica, infectando a más de 100 especies de mamíferos silvestres y domésticos. Actualmente, solo hay dos medicamentos antibióticos disponibles para el tratamiento de esta enfermedad, que son, benznidazol y nifurtimox. Sin embargo, el parásito *Trypanosoma cruzi* ha desarrollado resistencia contra estos medicamentos disponibles. Existe la necesidad de desarrollar nuevos fármacos para la prevención y tratamiento de la enfermedad de Chagas. La investigación demuestra que los compuestos botánicos pueden ser efectivos contra *T. cruzi*. Los botánicos han mostrado resultados potentes contra las etapas de tripomastigotes en sangre, epimastigotes, amastigotes y tripomastigotes de *T. cruzi*. Se ha demostrado que los compuestos botánicos como chalconas, fenólicos, alcaloides, terpenoides, ácidos benzoicos y quinonas tienen como objetivo directo a *T. cruzi*. Los mecanismos directos implican daño al ADN, alteración de las vías energéticas y disruptura de las membranas celulares.

**Palabras clave:** *T. cruzi*; Enfermedad de Chagas; Actividad anti-tripanosomal; Botánicos; Derivados de plantas

## INTRODUCTION

*Trypanosoma cruzi* belongs to the family Trypanosomatidae and is a kinetoplastid (special organelle kinetoplast containing) protozoan (Kostygov *et al*., 2021). *T. cruzi* is classified into 7 different discrete typing units. These discrete typing units (DTUs) include *T. cruzi* 1 (Tc1), Tc2, Tc3, Tc4, Tc5, Tc6, and Tcbat (Velasquez-Ortiz *et al*., 2022; Cáceres *et al*., 2024). These discrete typing units present different clinical, geographic, and epidemiological associations (Ledezma *et al*., 2020; Velasquez-Ortiz *et al*., 2022). The geographical distribution of DTUs varies widely, as Tc (1-6) are present frequently in Argentina, Chile, Paraguay, and Bolivia (Domagalska & Dujardin, 2020). The identification of these DTUs is based on specific genetic markers which can be checked with the help of polymerase chain reaction (PCR) (Breniere *et al*., 2016). The mini-exon gene is responsible for the differentiation among multiple discrete typing units. The disease transmitted by *T. cruzi* is termed Chagas disease in humans, also known as American trypanosomiasis (Conrad, 2021). Chagas disease is named after Brazilian physician Carlos Chagas, who discovered this parasite while working in his laboratory at the Oswaldo Cruz Institute, Brazil in 1909 (Chao *et al*., 2020). Chagas disease is known for causing serious problems including a high number of mortalities and morbidities in various parts of the world but more specifically in Latin America (Guhl & Ramirez, 2021). This disease infects about 6-8 million people annually with thousands of annual mortalities (Martin-Escolano *et al*., 2022), while 65-100 million people are at risk of getting an infection around the globe (Chastonay & Chastonay, 2022; Vascones-Gonzalez *et al*., 2023). Chagas disease is a zoonotic disease that is found in multiple animal species and can be transmitted from one to another by the arthropod vector. *Trypanosoma cruzi* needs one vertebrate host (any animal of the mammalian group) and a vector (triatomine bug) to complete its life cycle. (Zuma *et al*., 2021). Humans and animals acquire infection through direct contact with the excreta/feces of infected bugs of *Triatoma* genus (Schaub, 2021). Blood transfusion, breastmilk feeding, vertical transmission, organ transplant, contaminated food, and placental route are the other sources of Chagas disease (Abras *et al*., 2022). The acute form of Chagas disease may last for some weeks to months, while the chronic form lasts for many years, maybe for decades (Lopez-Velez *et al*., 2020). Acute form includes fatigue, rash, fever, and flu-like symptoms. Chronic form of Chagas disease is more serious and severe health problems can occur, including digestive and heart problems, leading to life-threatening complications (Medina-Rincon *et al*., 2021). Neurological symptoms may occasionally be involved in the severe forms of this disease (Useche *et al*., 2022). Because of these issues, control of *T. cruzi* is a primary concern for scientists.

Control of *T. cruzi* chiefly depends upon the therapeutic use of two groups of antibiotics: Benznidazole and Nifurtimox (Ramos *et al*., 2024). These classes are a primary source of treating Chagas disease in humans and animals. Both drugs are still in practice, but resistance-related issues necessitate their alternatives. A major problem with using antibiotics and chemotherapeutic medicines is the development of resistance (Nanayakkara *et al*., 2021; Saeed & Alkheraije, 2023; Ullah *et al*., 2023; Baz *et al*., 2024). This resistance against anti-trypanosomal agents is causing a threat to public health (Kasozi *et al*., 2022). Antibiotics also have several other problems, i.e., drug residues, public health concerns, environmental contamination, etc. (Hurkacz *et al*., 2021). Benznidazole and Nifurtimox have a limitation in that they are only effective in the early stages of Chagas disease and if the disease progresses, they show no effects (Rolon *et al*., 2022). In this scenario, the principal focus of scientists is to control this disease through preventive and alternate measures.

Preventive therapies are also being tried, but antiparasitic vaccination is not a successful tool to be used, especially in vector-borne diseases (Ahmad *et al*., 2022; Nepveu-Traversy *et al*., 2024). Vaccination to prevent the disease is a possible option, but most of the time vaccines don't work because of the various morphological forms of the parasite (Martin-Escolano *et al*., 2022). Currently, there is no vaccine available in the market for the control of Chagas disease (Camargo *et al*., 2022). Vector elimination may be a successful strategy, but the inhabitants and travelers to endemic areas may acquire this disease upon exposure to bugs.

Because of issues with current control and prevention strategies, there is a need to find suitable alternatives to having anti-trypanosomal activity (Murta *et al*., 2024). Multiple alternatives are being suggested, including prebiotics, probiotics, peptides, immunogens, vitamins, and plant-based preparations. Among all the alternative substances, botanicals are the most prominent because they have diverse groups of biologically active compounds with proven

medicinal and antiparasitic activities (de Albuquerque *et al*., 2020; Aljohani, 2023; Velazquez-Antunez *et al*., 2023; Eltaly *et al*., 2023; Ahmad *et al*., 2023; Batool *et al*., 2023). Plant metabolites have the potential to be used as therapeutic substances because of their wound healing, rehabilitation, anti-infectious, and antifungal activities (Hzounda *et al*., 2021; Mubashir *et al*., 2022; Ozuicli *et al*., 2023). Botanical compounds act as anti-inflammatory, antioxidant, anti-infectious, and immunomodulatory agents, they can also be used as growth promoters (Mohammad *et al*., 2023; Rehman *et al*., 2023). They have another major benefit, i.e., they are much safer to administer in the organism and lower toxicity problems (Mohamed & Hassan, 2023). Multiple groups of botanical compounds, i.e., phenolics, terpenes, chalcones, benzoic acids, and others have been proven in the research to have anti-trypanosomal activities (Espinosa-Bustos *et al*., 2020; Gonzalez *et al*., 2020a; Vasquez-Jimenez *et al*., 2021; Bonardi *et al*., 2022; Pardo-Rodriguez *et al*., 2022). Because of diverse mechanisms of action, botanicals can arrest multiple stages of parasites (Saeed & Alkheraije, 2023). This review focuses on the specific mechanism of action of plant-based compounds against the anti-trypanosomal activity, with a specific focus on the stage of the parasite being affected. Understanding the mechanism of actions of botanicals against *T. cruzi* demands a comprehensive overview of the life cycle and morphological stages of the parasite.

## METHODOLOGY

This review used Google Scholar (**www.scolar.google.com**) as the primary source of information. Furthermore, ResearchGate (**www.researchgate.com**), PubMed (**https://pubmed.ncbi.nlm.nih.gov**) and ScienceDirect (**http://www.sciencedirect.com**) were used as secondary search engines. Keywords used are "*Trypanosoma cruzi*", "Chagas disease", "Botanical control of *T. cruzi*", "phytochemicals used against *T. cruzi*", "Plants used for the control of *T. cruzi*", and "Use of herbal products against *T. cruzi*". This is a qualitative review, so no statistical comparison was made.

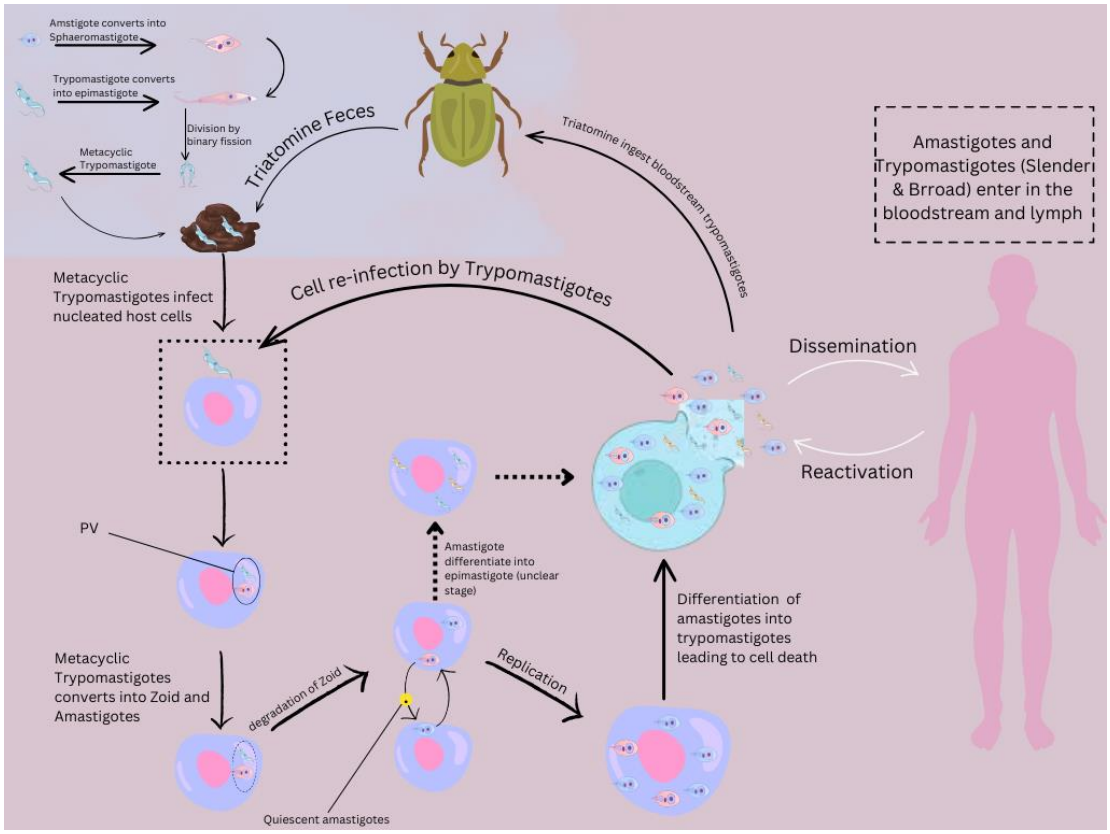
### Life cycle of *T. cruzi*

The classical life cycle of *T. cruzi* includes a mammalian host and a vector (triatomine bug) (Martin-Escolano *et al*., 2022). Infection in the mammalian host begins with metacyclic trypomastigotes, which are non-dividing in nature (Oliveira *et al*., 2020). The infected metacyclic trypomastigotes are present in the waste/excreta of the triatomine bug (Schaub *et al*., 2011). Trypomastigotes enter the host through any kind of rupture in the surface membrane, mostly because of the bite of the vector (Rodrigues *et al*., 2013). Many phagocytic and non-phagocytic cells provide binding sites to these trypomastigotes (Rodriguez-Bejarano *et al*., 2021). After binding, they enter a membrane-bound vacuole which is known as a Parastiophorous vacuole (PV). In PV, these parasites discriminate into round-shaped small amastigotes (Najera *et al*., 2021). After this differentiation, these amastigotes move from PV to the cytoplasm of the host cell, where all the other morphological changes occur, including flagella formation (Taylor *et al*., 2020). Now, the small amastigotes are further divided by binary fission, and the complete cell gets filled with these parasites (Barrias *et al*., 2022). After filling the complete space of the cell, the process of elongation starts, which is characterized by a large flagellum and converts it into a non-replicative form known as trypomastigotes. These trypomastigotes cause the lysis of the cell membrane of the host because of their intense movements and circulate continuously in the cell (Ferri & Edreira, 2021). After rupturing the cell membrane, trypomastigotes invade the neighboring cells. Trypomastigotes also enter the blood and lymph of the host and are named bloodstream trypomastigotes (BTs). BTs are now taken up by the triatomine bugs when they start sucking the blood of the host (Melo *et al*., 2020). Trypomastigotes now start to convert into epimastigotes in the mid-gut of the vector. In the final stage, which is metacyclic trypomastigotes, they move from the mid-gut to the hindgut of the bug (Povelones *et al*., 2023). They get attached with the help of their long flagellum to the waxy gut cuticle (Figure No. 1) (Martin-Escolano *et al*., 2022). The life cycle depicts that *T. cruzi* changes its morphological form continuously and the change of this form affects the mechanisms of drug actions difficult (de Lima *et al*., 2020), so understanding the various forms of *T. cruzi* is crucial before proceeding to the anti-trypanosomal substances and their mechanisms of actions.

#### *Morphological forms*

*Trypanosoma cruzi* has multiple morphological forms at different stages of its life cycle (Tyler *et al*., 2003). These morphological forms include amastigote, epimastigote, metacyclic trypomastigote, quiescent

amastigote, sphaeromatigote, and zoid. The amastigote stage is present in both triatomine bugs and mammals as well. This form of *T. cruzi* is present in the stomach, blood, and target tissues (Lainson *et al*., 1979; Dumoulin & Burleigh, 2021). Epimastigote stage is an intermediate stage between amastigotes and trypomastigotes. Both mammals and triatomine bugs may have this parasitic stage, but its presence has not been confirmed in mammals (Martin-Escolano *et al*., 2022). Metacyclic trypomastigote is an infective form during the early stage of disease in mammals and it is the stage transmitted by the bug to mammals. Trypomastigotes are found in the blood of mammals, and hindgut and excreta of the bug. The zoid form is just a cell having no nucleus, and it is only present in mammals. They are quickly degraded (taken up by the host) and do not have any association with the life cycle or pathogenesis of *T. cruzi* (Taylor *et al*., 2020). Dormant amastigote, which is also known as quiescent amastigote, is an intra-cellular and non-replicative form of *Trypanosoma* (Campetella *et al*., 2020). Bloodstream trypomastigotes (BTs) have 2 morphological forms, broad and slender. Broad BTs are present in mammals and triatomine. They are present in the lymph, blood, and stomach (Tetaud *et al*., 1997). They can stay for a longer duration in the bloodstream (Ward *et al*., 2020). Slender BTs are also present in mammals and triatomine bugs, but they can cause more infection as compared to Broad BTs (Martin-Escolano *et al*., 2022). They can cause infection by two methods: phagocytosis and penetration (Rodriguez-Bejarano *et al*., 2021). All the trypomastigotes are very sensitive to the drugs (Mazzeti *et al*., 2021). They are also extra-cellular and non-replicative in nature, present in blood, stomach, and lymph (Zuma *et al*., 2021). Sphaeromastigotes are another form of *T. cruzi* present only in triatomine bugs (Schaub, 2024). They do not have any acute or chronic form in mammals (Misra *et al*., 2016). Mostly they are present in the mid-gut of the bug, and they are non-replicative (Figure No. 2) (Martin-Escolano, 2020). These morphological forms provide an understanding that botanicals can be used only for those forms that are present in the mammalian host, helping in understanding the mechanism of action against specific morphological stages.




**Figgure No. 1**
**Life cycle of *T. cruzi* in the mammal host and vector**

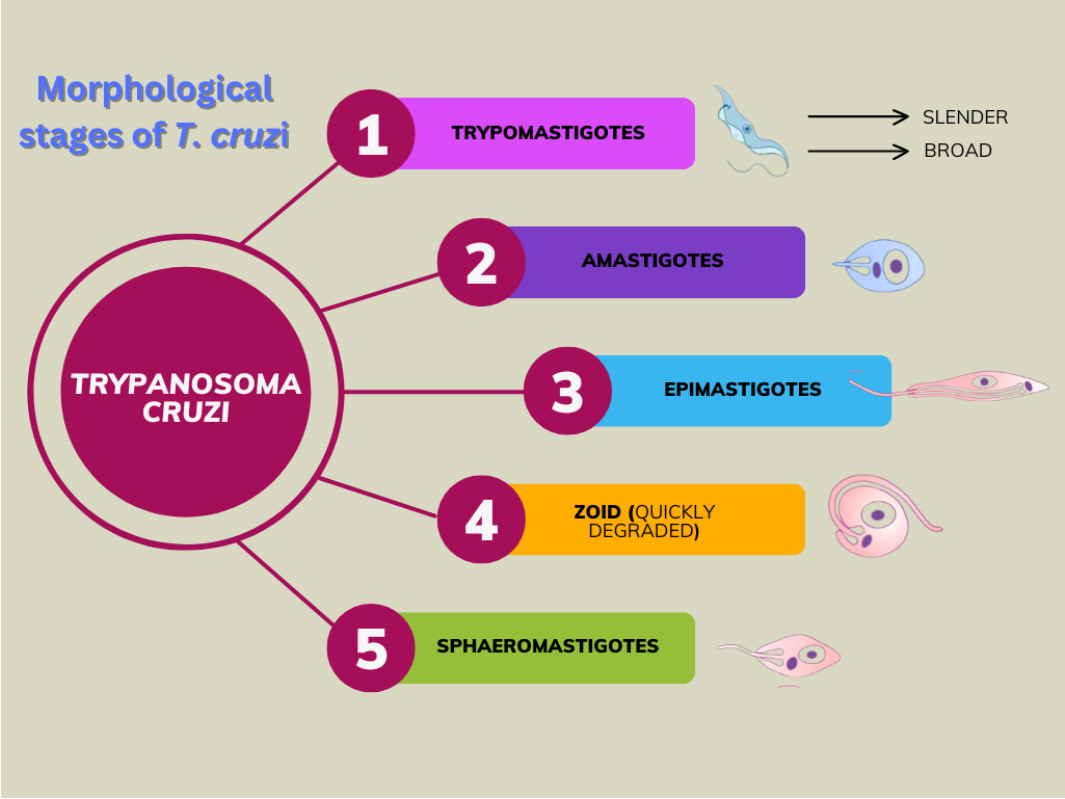



**Figure No. 2**
**Morphological stages of *T. cruzi***

**Table No. 1**
**Shape, location, and host of different morphological forms of *T. cruzi***

| Morphological Form | Shape | Location | Host | Flagellum | References |
|---|---|---|---|---|---|
| Amastigote | Rounded or oval | Targeted organs, blood, and stomach | Mammal/ Triatomine | Absent | Alves & Bastin, 2023 |
| Epimastigote | Spindled and elongated | Midgut and targeted organs (unclear) | Triatomine/ Mammal (unclear) | Present | Nascimento *et al*., 2022 |
| Metacyclic trypomastigote | Elongated and slender | Hindgut, excreta, and blood | Triatomine/ Mammal | Present | Halliday *et al*., 2021 |
| Zoid | Round | Not specific | Mammal | Absent | Martin-Escolano *et al*., 2022 |
| Quiescent amastigote | Not specific | Targeted organs | Mammal | Absent | Martin-Escolano *et al*., 2022 |
| Broad Bloodstream trypomastigotes | Pleomorphic | Blood, lymph, and stomach | Triatomine/ Mammalian | present | Barrias *et al*., 2022 |

| | | | | | |
|---|---|---|---|---|---|
| Slender Bloodstream trypomastigotes | Pleomorphic or similar to the metacyclic form | Blood, lymph, and stomach | Triatomine/ Mammalian | Present | Barrias *et al*., 2022 |
| Sphaeromastigotes | Irregular shape | Midgut | Triatomine | Present | Ferella, 2008<br>Taylor *et al*., 2021 |

***Botanical compounds used against T. cruzi***

Botanical compounds have been proven effective for their medicinal effects and the control of multiple parasites (Nawaz *et al*., 2022; Al-Saeed *et al*., 2023; Hussain *et al*., 2023; Al-Hoshani *et al*., 2023; Ghazy *et al*., 2023; Swantara *et al*., 2023). Various types of botanical agents have been tried for the control of *T. cruzi* in animals and humans. Some groups of botanical compounds have been found ideal to be used for clinical and therapeutic studies. The mechanism of action of these drugs against *T. cruzi* and their effects are discussed in the following sections.

***Chalcones***

Chalcones are plant-based polyphenolic compounds belonging to the flavonoids (Singh *et al*., 2020). Chalcones are unsaturated ketones having two aromatic rings attached to a 3-carbon alkenone unit (Bovonsambat *et al*., 2022). Chalcones are highly attractive anti-trypanosomal agents, because of their simple structure and promising biological applications (Henriquez-Figuereo *et al*., 2023). They have a wide range of antibacterial, antifungal, antiprotozoal, and antiproliferative pharmacological activities (Goyal *et al*., 2021; Al-Khayri *et al*., 2023).

Chalcones have shown anti-trypanosomal activity in multiple research studies (Zulu *et al*., 2020; N'Guessan *et al*., 2021; Zheoat *et al*., 2021; Cuellar *et al*., 2022; Magalhaes *et al*., 2022; Gomes *et al*., 2023; Setshedi *et al*., 2024). Researchers have reported that chalcones are effective against amastigotes and trypomastigotes stage (Passalacqua *et al*., 2015; Gonzalez *et al*., 2020b). Chalcones affect the glycolysis pathways of the trypomastigote stage of *T. cruzi* (Beltran-Hortelano *et al*., 2022). Trypomastigotes present in the bloodstream can't produce energy by any other mechanism. They have glycosomes that are responsible for the glycolysis in the cell and perform glycolysis or gluconeogenesis, according to need (Michels *et al*., 2000). ATP production by glycolysis is mandatory for the survival of *T. cruzi* at the trypomastigote stage. Glycolytic enzymes have been reported to be targeted to control trypomastigotes of *T. cruzi* by different types of chalcones (Goncalves *et al*., 2011; Saraiva *et al*., 2022). Chalcones can Inhibit *T. cruzi* glycosomal glyceraldehyde-3-phosphate dehydrogenase (GAPDH), by disturbing the energy mechanism of the cell, as reported by Tomazela *et al*. (2000).

Another mechanism of the action of chalcones is by acting on curzain (Borchhardt *et al*., 2010). Cruzain is a cysteine protease of *T. cruzi* which is chiefly responsible for the invasion of trypomastigotes into the host cell (Aparicio *et al*., 2004; Nascimento *et al*., 2021). It is also associated with providing nutrition, metabolism, metacyclogenesis, infectivity, and multiplication of trypomastigotes in the host cells (Losinno *et al*., 2021). Multiple studies have reported chalcones to target cruzain for the inhibition of the trypomastigotes of *T. cruzi* (Borchhardt *et al*., 2010; Gomes *et al*., 2014; de Brito *et al*., 2022; de Oliveira *et al*., 2022; Magalhaes *et al*., 2022; Matos *et al*., 2022; Cavalcante *et al*., 2023; Gomes *et al*., 2023). Blockage of cruzain causes death of *T. cruzi* in trypomastigote and amastigote stages (Mazzeti *et al*., 2021). Control of *T. cruzi* by chalcones and derivatives has been proven effective and they can be used to synthesize potent drugs. An overview of chalcones used for control of *T. cruzi* has been given in Table No. 2.

***Benzoic acids***

Benzoic acids are plant compounds that have a benzene ring with at least one carboxyl group attached to it (Godlewska-Zylkiewics *et al*., 2020). Trypomastigote is the most critical stage because it is involved in the basic pathology of Chagas disease (Lopez-Velez *et al*., 2020). It is an invasive stage and is marked by the sialidase enzymes present in its structure (Campetella *et al*., 2020). These enzymes help attach the cells and invade inside the cells (Keil *et al*., 2022). Benzoic acids control *T. cruzi* by inhibiting the sialidase enzyme (Cristovao-Silva *et al*., 2024). Sialidase enzyme is the main pathogenic

enzyme of the trypomastigote form. It is responsible for the attachment of *T. cruzi* to the host cells because of sialic acid mechanisms (Rodriguez-Bejarano *et al*., 2021). Benzoic acids have 'meta' and 'para' functional groups which diversify their medicinal activities (Du *et al*., 2023). The 'meta' and 'para' rings attached to their phenolic structure provide negatively charged hydroxyl groups and they can work as analogs of sialic acids (Simone *et al*., 2022). This stops the conversion of sialidase into sialic acids as well as blocks attachment to the host cells. Benzoic acids in this way block trans-sialidase enzymes which can't be formed in the trypomastigote stage (Neres *et al*., 2007). So, *T. cruzi* can't attach to the host cell and becomes prone to the immune system. The activity of benzoic acid can be enhanced by the addition of a sucrose base or glycoconjugate of sialic acids (Robinson, 2020). Multiple researchers have reported the effectiveness of benzoic acids and their derivatives against the control of *T. cruzi* (Neres *et al*., 2007; Flores *et al*., 2008; Flores *et al*., 2009; Correa *et al*., 2012; Kashif *et al*., 2017; Vazquez-Jimenez *et al*., 2019; Cuevas-Hernandez *et al*., 2020). Benzoic acids and derivatives can be used to formulate new synthetic drugs for the treatment and control of *T. cruzi* (Table No. 2).

***Quinones***

Quinones are cyclic organic compounds having a conjugated system of carbonyl groups (Go *et al*., 2024). They are well known for their antioxidant and redox properties (Jung *et al*., 2020). Trypanothione reductase enzyme is very crucial for the thiol-redox balance of *T. cruzi* (Piñeyro *et al*., 2021). Regulation of thiol-redox balance in the host cell is essential for the signaling, metabolic, and transcriptional processes (Specker *et al*., 2021). It plays a vital role in the defense mechanism of the parasite (Ali *et al*., 2022). Quinones have been reported to exhibit very effective results against the trypanothione reductase enzyme (Cenas *et al*., 1994; Salmon-Chemin *et al*., 2001; Zani & Fairlamb, 2003; Pinto & de Castro, 2009; Venkatesan *et al*., 2010; Vera *et al*., 2017; Lopez-Lira *et al*., 2021; Espinosa-Bustos *et al*., 2022; de Lucio *et al*., 2022; Rani *et al*., 2022). Quinones and derivatives counter the trypomastigote and epimastigote form of *T. cruzi* (Ballesteros-Casallas *et al*., 2023). Trypanocidal activity of the quinones has been claimed to have more selectivity and potent results as compared to the commercially available drug Nifurtimox (Rani *et al*., 2022). However, quinones showed activity against the BT stage of *T. cruzi* in a study by (Gonzalez *et al*., 2020a). After the critical analysis of different research on the anti-trypanocidal activity of quinones, we can say that quinones can be proved as an effective source for the development of new drugs against *T. cruzi*. An overview of the mechanism of action of quinones against different stages of *T. cruzi* is given in Table No. 2.

***Terpenoids***

Terpenoids are naturally occurring organic compounds containing a 5-carbon block, also known as an isoprene unit (Roba, 2020). They are named because of their strong-smelling property (Ben Salha *et al*., 2021). Attraction toward terpenoids is increasing day by day because of their remarkable antiparasitic, antiviral, cardiovascular, anti-inflammatory, and anti-cancer biological activities (Yang *et al*., 2020). Terpenoids have been already distributed commercially for the treatment of malaria and cancer (Dash *et al*., 2022). Multiple research experiments have been conducted on terpenoids for the treatment and control of *T. cruzi*, proving their potential against Chagas disease (Izumi *et al*., 2012; Ramirez-Macias *et al*., 2012; Ferreira *et al*., 2013; Vaz, 2017; de Rosa *et al*., 2020; Durao *et al*., 2022).

Terpenoids mainly affect the cysteines in *T. cruzi* (Pardo-Rodriguez *et al*., 2023a). Cysteine is a non-essential amino acid that is responsible for the metabolic functions and production of protein in *T. cruzi* (Ali *et al*., 2022). It is the main building block of trypanothione which is responsible for the redox balance in the cell as described earlier (Arias *et al*., 2020). Cysteine synthase enzyme is present in the cytoplasm, mitochondria, and chloroplast of the cell, which is necessary for cysteine production (Wirtz *et al*., 2023). Terpenoids block the synthesis of cysteine synthase, which disturbs the redox balance of the cell, ultimately causing cell death (Kamran *et al*., 2022). Terpenoids have extensive trypanocidal activity in different morphological forms of the parasite i.e. amastigotes, trypomastigotes, and epimastigotes (Veas *et al*., 2020). Commercial drugs against *T. cruzi* can be made using terpenoids as there are already some terpenoid-based drugs available against other diseases, as described earlier.

***Alkaloids***

Alkaloids are organic compounds that have at least one nitrogen atom attached to them (Dey *et al*., 2020). Information regarding the mechanism of action of alkaloids against protozoa is scant in the literature (Martinez-Peinado *et al*., 2022). However, alkaloids have been reported to demonstrate great

antioxidant properties (Li *et al*., 2020; Adedayo *et al*., 2021). The antioxidant activity of alkaloids causes inhibition of the growth and respiration of *T. cruzi* (Martinez-Peinado *et al*., 2022). Alkaloids inhibit cellular respiration, which indicates the possibility that they may disrupt or block the electron transport chain of mitochondria (Fakhri *et al*., 2021). Multiple researchers have reported that the use of alkaloids and their derivative compounds proved effective against the different morphological forms of *T. cruzi* (Chataing *et al*., 1998; Silva *et al*., 2020; da Rosa *et al*., 2022; Barbosa *et al*., 2023; Bosch-Navarrete *et al*., 2023).

***Phenolics***

Phenolics are plant-based heterogeneous compounds that have hydroxyl groups attached to the benzene ring (Santos-Buelga *et al*., 2019). Phenolics can alter the permeability of the plasma membrane and the integrity of the cell membrane of *T. cruzi* (Menna-Barreto *et al*., 2009; Galvao *et al*., 2021). Change in the plasma membrane permeability allows the intracellular contents released out of the cell, resulting in the activation of the immune response of the host cell (Dias & Nylandsted, 2021). Activation of the immune response of the host cell ultimately causes the death of invading *T. cruzi* (Cerban *et al*., 2020). Multiple researchers have reported the anti-trypanocidal activity of phenolics and they have less cytotoxic effects (Jimoh *et al*., 2020; Galvao *et al*., 2021; Sousa *et al*., 2023). However, phenolics can act on the different stages of *T. cruzi* explained in Table No. 2. The exact mechanism of action of phenolics against *T. cruzi* is scant in the literature.

**Table No. 2**

**Major groups of botanicals, their mechanism of action, and effects on various stages of *T. cruzi***

| Sr. no. | Botanical | Mechanism of actions | Compound used | Parasite Stage | Results | References |
|---|---|---|---|---|---|---|
| 1. | Chalcones | Inhibits *T. cruzi* glycosomal glyceraldehyde-3-phosphate dehydrogenase. It also inhibits the curzain enzyme of *T. cruzi*. | Coumarou-chalcone | Amastigote | Chalcones arrest different morphological forms of *T. cruzi* resulting in the death of *T. cruzi.* | Cuellar *et al*., 2022 |
| | | | Pyrano chalcone | Epimastigote | | (Tomazela *et al*., 2000) |
| | | | Thiophene chalcone | Amastigote | | De Oliveira *et al*., 2022 |
| | | | Prenyloxy chalcones | Epimastigote | | Espinoza-Hicks *et al*., 2019 |
| | | | 2-hydroxy-3,4,6-tri methoxyphenyl chalcones | Amastigote | | Magalhaes *et al*., 2022 |
| 2. | Benzoic acids | Inhibition of Trans-sialidase enzyme | *Para*-aminobenzoic acid | Trypomastigote | Trypanocidal activity has been observed after the use of benzoic acids and their derivatives. | Kashif *et al*., 2017 |
| | | | L-Bornyl benzoate | Epimastigote | | Correa *et al*., 2012 |
| | | | 4-amino-3-nitrobenzoic acid | -do- | | Vazquez-Jimenez *et al*., 2019 |
| | | | Trimethyl-bicyclo- tri methoxy-benzoate | -do- | | Zielinska-Blajet & Feder-Kubis, 2020 |
| | | | Trimethyl-bicyclo-benzoate | -do- | | Zielinska-Blajet & Feder-Kubis, 2020 |
| 3. | Quinones | Binds with *T. cruzi* trypanothione reductase, Inhibition of DNA & RNA | Komaroviquinone | Trypomastigote | Kills a variety of *T. cruzi*'s morphological forms at different stages. | Suto *et al*., 2015 |
| | | | Napthoquinones | Epimastigote, Trypomastigote, and Bloodstream trypomastigote | | Salas *et al*., 2011 |
| | | | Furanequinone | Amastigote | | Ballesteros-Casallas *et al*., 2023 |
| | | | Thiazolequinone | -do- | | Pathak *et al*., 2023 |

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|---|---|---|---|---|---|---|
| 4. | Terpenoids | Inhibits cysteine synthase enzyme | Lupeol Acetate | Trypomastigote and Amastogote | Inhibits the growth of *T. cruzi* resulting in the death of protozoan. | Pardo-Rodriguez *et al*., 2023a |
| | | | Betulinic acid | Epimastigote and Trypomastigote | | Sousa *et al*., 2017 |
| | | | Pomolic acid | -do- | | Castañeda *et al*., 2021 |
| | | | Ursolic acid | -do- | | Pardo-Rodriguez *et al*., 2023b |
| | | | Rotundic acid, | -do- | | Castañeda *et al*., 2021 |
| 5. | Alkaloids | Anti-*Trypanosoma cruzi* activity by blocking respiration | Aporphines | Epimastigote | Arrest different altering morphological forms of *T. cruzi*, ultimately death of the parasite. | Pieper *et al*., 2020 |
| | | | Naphthylisoquinolines | Trypomastigote | | Fernandez *et al*., 2021 |
| | | | Quinolinones | -do- | | Musiol *et al*., 2017 |
| | | | Furoquinolines | Epimastigote | | Belen Valdez *et al*., 2022 |
| | | | Indoles | -do- | | Cavin *et al*., 1987 |
| | | | Hippeastrine | Amastigote | | Martinez-Peinado *et al*., 2020 |
| | | | Guanidines | Trypomastigote | | Martins *et al*., 2016 |
| 6. | Phenolics | Change the permeability and integrity of the cell membrane | Vestitol | Epimastigote | Execute *T. cruzi* by changing the plasma membrane permeability. | Sousa *et al*., 2023 |
| | | | polyphenols | Bloodstream trypomastigote and amastigote | | Vargas-Munevar *et al*., 2024 |
| | | | Quercetin | Amastigote | | Faria *et al*., 2017 |

## CONCLUSION

*T. cruzi* is a major threat to human health by spreading Chagas disease. Only two drugs (Benznidazole and Nifrutimox) are commercially available for controlling the spread of disease. There is a need for new drugs to be introduced because of the day-by-day increasing resistance to available drugs. Botanicals have been proven effective against *T. cruzi* including chalcones, benzoic acids, quinones, terpenes, alkaloids, and phenolics. The detailed mechanisms of action of these botanical compounds have shown their effectiveness against *T. cruzi.* The organic compounds derived from different plant sources were tested against trypomastigotes, amastigotes, BTs, and epimastigotes of *T. cruzi* and had proven positive effects. We can conclude from our review that these plant-based organic compounds may be a better option to replace the antibiotics from which resistance has been developed. However, further research must be conducted on these compounds to check the safety index, their toxic and harmful effects on consumer health. The development of new potent drugs for the prevention and control of T. cruzi will help the clinician for better treatment alternative and prevent antimicrobial resistance.

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