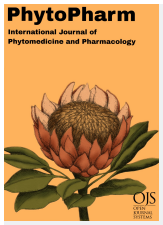

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Artemisia Species as Antitrypanosomal Agents: Treatment Challenges in African Trypanosomiasis and Chagas Disease

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ABSTRACT
Trypanosomiasis is a serious public health issue in tropical and subtropical areas and is brought on by a group of parasites that are transmitted by insects. *Trypanosoma brucei*, which causes human African trypanosomiasis, and *Trypanosoma cruzi*, which causes Chagas disease, are the two main species that affect people. Only a few medications are available for the treatment and prevention of these infections, and these medications have significant limitations including severe side effects, prolonged treatment times, low efficacy, and the emergence of drug-resistant strains. Better treatments are therefore urgently required. Some *Artemisia* spp. have shown mild cytotoxicity toward mammalian cells as well as antiparasitic action, including antitrypanosomal activity. They are an encouraging source for the identification of novel therapeutic agents for neglected tropical diseases in underdeveloped nations. In this review, the focus is to highlight the findings of recent studies on the activity of *Artemisia* spp. against trypanosomes as well as isolated compounds that have shown antitrypanosomal potential. All *Artemisia* spp. with reported antitrypanosomal activity are included in this review as well as literature regarding the antiparasitic potential of common *Artemisia* spp. This review has been compiled by searching major databases including Google Scholar, Web of Science, Scopus, PubMed, EBSCOhost, and Science Direct.

1. Introduction

1.1 Trypanosomal disease burden

Trypanosomiasis is a significant neglected tropical disease affecting humans and livestock in the tropics (Brun et al., 2010). It is primarily driven by two species: *Trypanosoma brucei*, which leads to Human African Trypanosomiasis (HAT), and *Trypanosoma cruzi*, the agent responsible for Chagas disease (CD). Both species are vector-borne and remain critical targets for global health interventions (Steverding, 2014; WHO, 2021b). The distribution of HAT is limited to sub-Saharan Africa, where appropriate habitats for its vector, the tsetse fly, occurs (Brun et al., 2010). Many of the affected populations live in remote rural areas with inadequate access to health care services, which complicates the surveillance and hence the diagnosis and treatment of this disease (WHO, 2020, 2021a, 2021c). War, poverty, and population displacement are other significant variables that aid in HAT transmission (WHO, 2021c). *Trypanosoma brucei gambiense* (*T. b. gambiense*) causes human disease in central and west Africa; *T. b. rhodesiense* in southern and eastern Africa; and *T. b. brucei* typically infects animals (Brun et al., 2010; Franco et al., 2014). The disease primarily affects poor people in remote rural areas of 36 Sub-Saharan African countries, where healthcare systems are frequently inadequate (Kennedy, 2019). HAT is thought to be a threat to 65 million people (WHO, 2021b).

CD is another life-threatening disease and is common in parts of Mexico, Central and South America (CDC, 2021). Endemic to 21 continental Latin American countries, CD is primarily transmitted to humans via the excreta (feces or urine) of infected triatomine insects. These hemipterans, colloquially referred to as 'kissing bugs,' serve as the principal vector for the dissemination of the *T. cruzi* parasite (WHO, 2020). There are currently three morphogenic forms of the *T. cruzi* parasite; trypomastigotes which are extracellular non-dividing forms, intracellular replicative amastigotes found in mammalian hosts and epimastigotes which divide in the midgut of reduviids (Tanowitz et al., 1992). Human population mobility, the existence of numerous triatomine subspecies, and poorly constructed homes, which gives way to cracks, provide an ideal habitat for the vector in Latin America's rural areas and sub-

urban slums are all factors that fuel CD transmission (WHO, 2021a). While the estimated global prevalence of *T. cruzi* infection dropped from 18 million in 1991 to 5.7 million in 2010—following the implementation of the first regional control initiatives—CD remains the most impactful parasitic pathology in the Western Hemisphere. Currently, CD is a global health problem affecting 6-8 million people (Lidani et al., 2019; CDC, 2020) and kills 12-14 thousand people per year (PAHO, 2021), and it is estimated that 70-100 million people are at risk of developing CD due to population mobility, most of them in Latin America (Lidani et al., 2019).

1.2 Current treatment options

Current chemotherapies for trypanosomiasis treatment in general face several challenges: drugs for HAT must be effective against two subspecies of *T. brucei* and against the disease's two stages of development. To meet these demands, chemotherapy must be tailored to each individual case, which means that different drugs must be used for the various stages of disease development as well as for the parasite in question (Gehrig and Efferth, 2008). Furthermore, drugs for the disease have varying degrees of toxicity; for example, melarsoprol, the only drug effective for treating the encephalitic stage of the disease in both subspecies of HAT, is highly toxic and fatal in 1-5% of patients, severely limiting its use and making it painful to administer (Büscher et al., 2017). The therapeutic management of HAT is characterized by prolonged hospitalization and severe drug-induced toxicity across nearly the entire current pharmacopeia. Coupled with the rising prevalence of drug-resistant strains, there is an urgent imperative to develop novel, safe, and more efficacious antitrypanosomal agents (Barrett and Croft, 2012).

For the treatment of CD, only two medicines, benznidazole and nifurtimox, both nitroheterocycles, are suggested (Barrett and Croft, 2012; WHO, 2020). They were developed more than 50 years ago but have several disadvantages such as severe side effects, long treatment periods, and regular treatment failures (Bern, 2015). According to the WHO (2020), both drugs are effective if administered shortly after an infection, at the onset of the acute phase. Both, however, lose efficacy as the disease progresses. In clinical practice, the therapeutic benefits of preventing CD progression must be carefully balanced against the lengthy treatment regimens and the high incidence of adverse events, which affect up to 40% of the adult patient population (WHO, 2020, 2021a). The nitroimidazole derivative benznidazole, which is more trypanocidal than nifurtimox, has significant adverse effects on the skin. Exfoliative dermatitis or dermatitis associated with fever and lymphadenopathy requires immediate cessation of administration of the drug (Bern et al., 2011). Bone marrow suppression, which is even more serious, prompts immediate interruption of treatment (Bern et al., 2011; CDC, 2021). Moreover, both medications are contraindicated in expectant women and individuals with kidney or liver failure. Nifurtimox is also not recommended for people with a background of neurological or psychiatric disorders (WHO, 2021a).

These therapeutic limitations provide a compelling incentive to identify novel treatments for both HAT and CD. New drug candidates must not only demonstrate safety and efficacy but also utilize distinct mechanisms of action to circumvent existing cross-resistance, which frequently occurs among structurally related derivatives (Gehrig and Efferth, 2008; Martín-Escolano et al., 2020). Bioprospecting for plant-derived metabolites offers a strategic pathway to mitigate systemic toxicity and delay the onset of resistance. Of particular interest are secondary metabolites that exhibit high trypanocidal specificity without associated general cytotoxicity (Gehrig and Efferth, 2008).

2. The genus *Artemisia*. A brief overview

A genus of interest that may contain interesting new drug leads is *Artemisia*, which is well known for producing the antiplasmodial compound artemisinin. Artemisinin and its derivatives have been shown to possess activity against other parasites such as *Trypanosoma* spp. In this review, the focus is on *Artemisia* spp. that have been shown to possess antitrypanosomal activity. *Artemisia afra* Jacq. ex Willd., *Artemisia annua* L., *Artemisia absinthium* L. and *Artemisia abyssinica* Sch.Bip. ex A.Rich. have been studied reasonably well and their general traditional medicinal use and all scientific studies of both *in vitro* and *in vivo* antitrypanosomal activity will be discussed. In addition, all *Artemisia* spp. where only limited studies have been conducted, and the general antiparasitic activity of promising *Artemisia* spp., but with no antitrypanosomal studies, will also be discussed. The species in this section includes *Artemisia abrotanum* L., *Artemisia capillaris* Thunb., *Artemisia arborescens* L., *Artemisia dracunculus* L., *Artemisia ludoviciana* Nutt., *Artemisia scoparia* Waldst. & Kit., and *Artemisia vulgaris* L.

Artemisia is a genus of herbs and shrubs belonging to the family Asteraceae, one of the most numerous plant groupings, and is found throughout the world (Abad et al., 2012). There are approximately 400 species distributed across Asia, Europe, and North America. The genus *Artemisia* exhibits its greatest diversity in Asia, with China and Japan hosting 150 and 50 species, respectively, while Russia contains approximately 174 indigenous taxa (Taleghani et al., 2020). In Southern and Eastern Africa, *A. afra* is the predominant species, spanning the mountainous regions of Kenya, Tanzania, and Uganda, and extending north into Ethiopia; its distribution also encompasses South Africa, Namibia, and Zimbabwe (Liu et al., 2009; Kane et al., 2019). Although less represented, several species are also indigenous to South America (Abad et al., 2012). Morphologically, the genus is highly diverse, comprising annual, biennial, or perennial herbs and shrubs. These plants are typically characterized by their aromatic profile and exhibit growth habits ranging from upright or ascending to occasionally decumbent stems (Taleghani et al., 2020). Studies of the phytochemistry of *Artemisia* have led to the identification of many compounds as well as essential oils (Abad et al., 2012), with almost six hundred compounds that have been characterised from *A. annua* alone (Brown, 2010). Phytochemical reports on *Artemisia* indi-

cate that this genus contains chemical constituents such as terpenoids, phenolics, coumarins, steroids, flavonoids, monoterpenoids, triterpenoids, sesquiterpenoids, and sesquiterpene lactones (Shahrajabian et al., 2020). The phytochemical constituents differ between the different species of *Artemisia*, as well as within the same species when collected from different geographical regions (Bilia et al., 2014; Zhang et al., 2017). These differences, which in fact influence the traditional medicinal application in different locations, are due to the impact of environmental stressors as secondary metabolites are biosynthesised in plants for adaptation to survive different environmental conditions (Zhang et al., 2017). The genus *Artemisia* includes many medicinal herbs which are currently the subject of scientific investigation due to their biological and chemical diversity. *Artemisia annua* and *A. afra* are prominent therapeutic agents in Asia and Africa, traditionally used against malaria, inflammation, and infections of viral, bacterial, or fungal origin (Abad et al., 2012). Beyond these uses, literature and field data highlight their importance in the indigenous treatment of trypanosomiasis across the African continent (Freiburghaus et al., 1996; Nibret and Wink, 2010; Bashir et al., 2015).

3. The antitrypanosomal activity of *Artemisia* species

3.1 *Artemisia afra*

3.1.1. Botanical aspects and traditional use

Artemisia afra is known by many traditional names in different regions of Africa including African wormwood (English), Wilde als (Afrikaans), Umhlonyane (Xhosa, Zulu) and Lengana (Sotho, Tswana) in South Africa (Van Wyk et al., 1997; Van Wyk, 2013) and Koddoo-adi in Ethiopia (Abebe and Ayehu, 1993). This species is characterized as an upright, perennial woody shrub, typically reaching heights of 0.6 to 2.0 m. Its oval-shaped leaves possess a soft texture and produce a distinct, sweet fragrance (Van Wyk et al., 1997). *Artemisia afra* (Figure 1) is a versatile traditional remedy used for a wide array of ailments. It is primarily employed to treat respiratory issues such as coughs, colds, influenza, croup, and asthma, as well as gastrointestinal complaints including dyspepsia, colic, constipation, and loss of appetite. Additionally, its therapeutic scope extends to metabolic and inflammatory conditions like gout, diabetes, and malaria, alongside various renal and bladder disorders (Van Wyk et al., 1997; Van Wyk and Gericke, 2000; Liu et al., 2009; Du Toit and Van der Kooy, 2019). It is also widely used in combination with other herbal plants for the treatment of headaches, eye disease, tinea capitis, haematuria and stabbing pain (Abebe and Ayehu, 1993). Watt and Breyer-Brandwijk (1962) indicated that *A. afra* in combination with *Eucalyptus globulus* Labill. (Myrtaceae) is used to treat influenza and an infusion of *Lippia asperifolia* A.Rich. ex Marthe (Verbenaceae) in combination with *A. afra* is used as a formula to treat fevers, influenza, measles, and as a prophylactic against lung inflammations. Therapeutic administration of the plant varies by condition: steam inhalation of decocted leaves is employed for respiratory ailments and dysmenorrhea, while the direct insertion of fresh leaf tips into the nasal passage or dental cavities is used to alleviate coryza, headaches, and odontalgia. Furthermore, leaf poultices are applied topically to manage neuralgia and mumps-related swelling, or placed on the abdomen to mitigate infantile colic. A tincture made from leaves wetted by brandy is also claimed to be helpful in reducing colic (Watt and Breyer-Brandwijk, 1962) and it is also employed as a contraceptive agent (Desta, 1994).

Figure 1: Aerial parts of *A. afra*. Illustration from Jacquin, N. J. (1804, t. 467). Digitized image courtesy of the Missouri Botanical Garden's Peter H. Raven Library (CC-BY-NC 2.5; accessed via plantillustrations.org).

3.1.2. Antitrypanosomal activity

Nibret and Wink (2010) used extracts prepared from four *Artemisia* spp. growing in Ethiopia, and the pure compound artemisinin, and demonstrated that both dichloromethane (DCM) and methanol extracts of *A. afra* were active against bloodstream forms of *T. b. brucei*. The IC_{50} for the extracts were found to be 77.54 and 25.27 µg/mL with selectivity indices of 5.08 and 4.87 for methanol and DCM extracts, respectively. Pure artemisinin only gave an IC_{50} value of 35.91 µg/mL with a selectivity index of 2.44. The study further noted that comparatively the DCM extract of *A. afra* was the second most active extract against *T. b. brucei* and was more active than the corresponding *A. annua* sample, the main source of artemisinin (Nibret and Wink, 2010). Mokoka et al. (2011) screened many plant species traditionally used in South Africa to treat malaria for *in vitro* activity against, amongst other parasites, *T. b. rhodesiense* and *T. cruzi*. The percentage inhibition at a concentration of 9.7 µg/mL against *T. b. rhodesiense* using DCM:Methanol

(1:1), DCM and methanol extracts were reported as 98, 97 and 96%, respectively. When screened against *T. cruzi* parasites, IC_{50} values of 54.3, 27.6 and 41.8 µg/mL for the extracts of *A. afra* were obtained, respectively. *Artemisia afra* have inhibitory activity towards trypanosomes and have been shown to be effective against *T. brucei*, *T. cruzi*, and *T. congolense* according to Nass and Efferth (2018). They also stated that this field of study is still in its infancy and that more research on the pharmacokinetics, bioavailability, and synergism among *Artemisia* spp. should be done (Nass and Efferth, 2018).

3.2 *Artemisia annua*

3.2.1. Botanical aspects and traditional use

Artemisia annua is native to China and grows naturally as part of the steppe vegetation in northern parts of the country. It is also cultivated on commercial scale in the eastern parts of the country, and more recently in India and Africa (Van Wyk and Wink, 2018). It is an aromatic annual herbaceous plant and can grow up to 2.4 m tall. The plant features an alternate leaf arrangement, with foliage ranging from deep green to brownish-green hues. It is further identified by its diminutive (1–2 mm) pale yellow inflorescences, which possess a distinctively pleasant fragrance (Dhingra et al., 1999). It is known by many names including Qinghao, Huang hua hao, wormwood, Chinese wormwood, sweet wormwood, annual wormwood, annual sagewort, annual mugwort, armoise annuelle and sweet sagewort (Bilia et al., 2008; Mesa et al., 2015; Zhang et al., 2017). *Artemisia annua* (Figure 2) is a well-known medicinal plant (Bhakuni et al., 2001) and is responsible for the production of the sesquiterpene lactone artemisinin, which is currently used to treat malaria in derivatised forms (Huang et al., 2009; Lee et al., 2023). It has been used for treating fever and malaria for more than 2,000 years in traditional Chinese medicine, earning a place in the Ethnopharmacopeia of Southeast Asia (Van Agtmael et al., 1999; Bilia et al., 2008). The herb sweet wormwood has been used to treat and prevent jaundice, haemorrhoids, and malaria (Zhang et al., 2017).

3.2.2. Antitrypanosomal activity

Research on the effectiveness of *A. annua* as well as artemisinin for the treatment of *Trypanosoma* has been reported. Using *A. annua* and pure artemisinin, Bilia et al. (2008) investigated the *in vitro* activities of *A. annua* extracts prepared using different solvent systems against *T. b. rhodesiense* and *T. cruzi* parasites. The results indicated that the acetone and n-hexane extracts of *A. annua* were the most active against *T. b. rhodesiense* with IC_{50} values of 0.300 and 0.455 µg/mL, respectively, while that of artemisinin was 24.400 µg/mL. According to the findings, acetone and hexane extracts had higher trypanocidal activity than pure artemisinin.

Figure 2: Artist's sketch of *A. annua*. Illustration by Jan Kops, originally published in Flora Batava, Vol. 9 (1846). Source: plantillustrations.org.

The amount of artemisinin in each extract also showed that the two most potent extracts did not have the highest concentrations. In addition, all the extracts showed some activity against *T. cruzi* (Bilia et al., 2008). A comparative study by de Morgado et al. (2017) examined the efficacy of *A. annua* infusions against *T. cruzi* epimastigotes, utilizing plant material sourced from both Venezuela and Luxembourg. Their findings revealed a dose-dependent inhibition of parasite proliferation, with the Luxembourg-derived infusion exhibiting significantly more potent trypanocidal activity. The inhibitory activity of *A. annua* against a variety of parasites, including *T. brucei* and *T. cruzi*, has been the subject of substantial research. Additional literature on *Trypanosoma* is compiled in Table 1.

Table 1: *in vitro* and *in vivo* antitrypanosomal activity of *A. annua* extracts.

Extract	Species	Model	Result	Reference
Hexane & ethanol	*T. brucei*	*in vitro*	IC_{50}: 15.3 and 27.2 μg/mL; SI: >5.9 and 3.3	Malebo et al., 2009
DCM & methanol	*T. brucei*	*in vitro*	Dose dependant inhibition	Efferth et al., 2011
Alcoholic	*T. brucei*	*in vitro*	Inhibition of proliferation (95% at 33 μg/mL)	Worku et al., 2013
Tea infusion	*T. cruzi*	*in vitro*	Antiproliferative effects	de Morgado et al., 2017
Methanol	*T. b. rhodesiense*	*in vivo*	Prolonged survival rate	Peter et al., 2009
Methanol	*T. evansi*	*in vitro*	Antitrypanosomal activity	Bawm et al., 2010
DCM & methanol	*T. brucei*	*in vitro*	IC_{50}: 41.05 and 99.40 μg/mL; SI: 3.48 and 1.41	Nibret and Wink, 2010

3.3 *Artemisia absinthium*

3.3.1. Botanical aspects and traditional use

Artemisia absinthium is an aromatic, perennial shrub-like subshrub reaching up to 1 m tall. The leaves are spirally arranged, greenish-grey coloured above and white below (Goud et al., 2015; Abascal and Yarnell, 2020). A dense pubescence covers the plant, which is further distinguished by its intense and sharp odor profile (Amidon et al., 2014; Hussain et al., 2017).

The leaves have essential oil-secreting silver hairs/glandular trichomes that protect them against high temperatures and prolonged drought (Hayat et al., 2009; Koch, 2009). For centuries, *A. absinthium* (Figure 3) has been integrated into traditional medicine, particularly for the management of parasitic infections, febrile conditions, and gastrointestinal disorders (Amidon et al., 2014). Wormwood became very popular when it was used in recreational drinks in the 18th and early 19th centuries, but it developed a reputation for causing psychotic events called absinthism (Riahi et al., 2013). The common name "wormwood" reflects its long-standing reputation as a potent anthelmintic; for millennia, it has been utilized to eradicate intestinal parasites such as tapeworms, threadworms, and roundworms (Grieve, 2021).

Beyond its antiparasitic utility, the species is employed to manage chronic pyrexia, hepatic inflammation, and menstrual irregularities. Its pharmacological importance is recognized globally, with the entire plant serving as a primary material in Ayurveda, Homeopathy, Unani, and Siddha systems (Nikhat et al., 2013). Specifically, in Unani medicine, it is the key constituent of the "Afsanteen" formulation used for hepatitis, oedema, and persistent fevers (Ahamad, 2019), whereas in traditional Chinese medicine, its applications extend to oncology (Parekh et al., 2009). Ethnobotanical records indicate that the herb is traditionally utilized for a diverse array of conditions, ranging from gastrointestinal distress (anorexia, bloating, and stomach ailments) and musculoskeletal issues (back pain and fibromyalgia) to more complex pathologies such as atherosclerosis, sclerosis, and schistosomiasis (Guarrera, 2005). Furthermore, it is applied topically for skin wounds, herpes, and venomous bites. The plant's essential oil (EO) is particularly valued for its multifaceted pharmacological profile, exhibiting potent antimicrobial, anti-inflammatory, and neuroprotective properties. It also serves as a versatile therapeutic agent with documented anthelmintic, antitumoral, and hepatoprotective activities, alongside its use as a digestive stimulant and diuretic (Bora and Sharma, 2010; Msaada et al., 2015). Wichtl (2004) noted however, that the pharmacological activity of this species in many of these indications has not been scientifically confirmed.

Figure 3: *Artemisia absinthium*. Illustration from Fuchs (1543, t. 1). Public domain image accessed via plantillustrations.org.

3.3.2. Antitrypanosomal activity

Modern scientific research on the effectiveness of *A. absinthium* in the treatment of *Trypanosoma* has also been reported. Bailen et al. (2013) tested selected EOs obtained from *A. absinthium* collected in Spain and demonstrated that the EOs were active against *T. cruzi* at 100, 400, and 800 μg/mL concentrations. The main components identified in the EOs — *cis*-epoxyocimene, chrysanthenol, bornyl acetate and thujone — have not been reported as being active against *Trypanosoma* and therefore, further studies are needed to identify the compound(s) responsible for the plants' antiparasitic effects. Martínez-Díaz et al. (2015) investigated the antiparasitic and cytotoxicity of the EO obtained from *A. absinthium* and nine liquid chromatography fractions obtained from the EO on *T. cruzi*. The EO showed considerable growth inhibition on *T. cruzi* parasites of 100% at 800 μg/mL, 96% at 400 μg/mL and 83.6% at 200 μg/mL indicating a GI_{50} of 144.6 μg/mL, agreeing well with the results reported by Bailen et al. (2013). Furthermore, fractions 1 and 2 were the most active on *T. cruzi* with nearly 100% mortality at 100 μg/mL, and the two fractions also demonstrated selective antiparasitic activity as they were not cytotoxic against non-tumour cell lines. However, some of the isolated compounds in the EO were unable to fully account for the activities of the fractions and EO. They concluded that *trans*-caryophyllene, the primary component found in fraction 1, needs to be further investigated due to its antiparasitic activity against *T. cruzi* and 3,6-dihydrochamazulene, because of the activity of fraction 2 in which it was identified as the major compound (Martínez-Díaz et al., 2015).

Nibret and Wink (2010) investigated the *in vitro* antitrypanosomal activity of Ethiopian *A. absinthium* EOs obtained from leaves and aerial parts against bloodstream forms of *T. b. brucei*. The findings demonstrated that *A. absinthium* extracts exhibited superior antitrypanosomal potency compared to other *Artemisia* spp. taxa. Specifically, the methanol and DCM fractions yielded promising IC_{50} values of 27.90 and 27.05 μg/mL, respectively. The SIs were determined to be 2.07 and 5.08, respectively. In this study, like in many others, the bioactivities or the cytotoxicity of the extracts could not be attributed to specific classes of compounds or their combinations. They indicated that the good activity of the herb might be attributed to camphor and two major sesquiterpene lactones, absinthin and artabsin (Nibret and Wink, 2010).

3.4 *Artemisia abyssinica*

3.4.1. Botanical aspects and traditional use

Artemisia abyssinica is a fragrant, erect herb—occurring as an annual or short-lived perennial—that typically reaches heights of 30–60 cm. It is characterized by sparingly branched, grooved upper stems and alternate, grey-green leaves measuring 4–10 cm in length, which terminate in pale yellow flower heads. Geographically, the species is widely distributed across high-altitude plateaus (2200–3600 m) in Asia, Saudi Arabia, Yemen, Ethiopia, and Eritrea, where it frequently colonizes roadsides, alluvial plains, and fallow fields (Tariku et al., 2010; Letha et al., 2016). Several infectious and non-infectious disorders, including trypanosomiasis, respond well to it as a traditional remedy (Geyid et al., 2005; Yineger et al., 2007). Heart issues and coughing are treated with consuming boiled leaves in milk (Tadesse, 2014). It is also used to treat leprosy, syphilis, gonorrhoea, rabies, and tonsillitis (Geyid et al., 2005; Tadesse, 2014). Domestic animals with epilepsy can be treated with fresh root juice (Yineger et al., 2007). In Asiatic nations, *A. abyssinica* is employed as an anthelmintic, antispasmodic, antirheumatic, and antibacterial agent in traditional medicine (Abad et al., 2012). A fresh entire plant decoction is traditionally used to treat diabetes mellitus as well as headaches and acts as an insect repellent (Mossa, 1985). Additionally, Ethiopians use it as a mosquito repellent (Chhetri et al., 2015). Other sources have documented its traditional uses as an antileishmanial, antitrypanosomal, anthelmintic, antispasmodic, antirheumatic, and antibacterial agent (Abad et al., 2012; Chhetri et al., 2015).

3.4.2. Antitrypanosomal activity

Feyera et al. (2011) evaluated the *in vitro* antitrypanosomal activity of the hydromethanolic and DCM extracts of the aerial parts of *A. abyssinica* against *T. congolense* field isolates. Both plant extracts showed appreciable *in vitro* antitrypanosomal properties with the DCM extract exhibiting higher activity. It was observed that after incubation with the DCM extract, trypanosome motility was eliminated by immobilising or by killing the parasites within 18 and 40 min at 4 mg/mL and 2 mg/mL concentration levels, respectively. The hydromethanolic extract significantly immobilized the trypanosomes compared to the negative control (water), where the results showed that significant antitrypanosomal activity was achieved with motility completely absent after 35 min at 4 mg/mL concentration level (Feyera et al., 2011).

In a subsequent *in vivo* assessment, Feyera et al. (2014) investigated the efficacy of *A. abyssinica* crude extracts against *T. congolense* in a murine model. Their results indicated that a seven-day course of intraperitoneal administration significantly lowered parasitemia levels; specifically, this effect was observed with the DCM extract at dosages of 200 and 400 mg/kg, as well as the hydromethanolic extract at 400 mg/kg. The DCM extract at 400 mg/kg yielded the most significant findings, maintaining a suppressed parasite load from day 4 through day 14 post-infection. In comparison, the 200 mg/kg DCM dose resulted in a notable decrease in parasitemia specifically on days 6 and 8. Furthermore, the 400 mg/kg hydromethanolic extract showed a statistically significant reduction in parasite levels on days 6, 8, and 10 when compared to the infected, untreated control group (Feyera et al., 2014).

In an *in vitro* assessment of Ethiopian *Artemisia* spp., Nibret and Wink (2010) evaluated the antitrypanosomal potential of methanol and DCM extracts derived from foliar and aerial components. When screened against bloodstream forms of *T. b. brucei*, the DCM extract of *A. abyssinica* demonstrated superior activity, yielding an IC_{50} of 19.13 μg/mL and a selectivity index of 8.24. Conversely, the methanol extract exhibited significant cytotoxicity toward HL-60 cells; its selectivity index of 1.33 represented the lowest selectivity observed in the study, indicating a narrow therapeutic window (Nibret and Wink, 2010)

3.5 Other *Artemisia* spp. with reported activity against trypanosomes

Generally, studies conducted on various *Artemisia* spp. have displayed antitrypanosomal activity both *in vivo* and *in vitro*. Larrazabal-Fuentes et al. (2020) tested infusions prepared from *A. copa* Phil. against *T. cruzi* and reported LD_{50} values of 131.8 μg/mL. Nurbek et al. (2020) isolated 18 compounds, including 3 new sesquiterpenoids, from *A. sieversiana* Ehrh. ex Willd. and tested the most promising compounds against *T. congolense* and reported activities ranging between 2.9–90.2 μM. Sainz et al. (2019) tested the EO of *A. pedemontana* Balb. ex Loisel. against *T. cruzi* and reported 100% growth inhibition at a concentration of 200 μg/mL. Jimenez et al. (2014) isolated dehydroleucodine from *A. douglasiana* Besser ex Besser and tested its activity against *T. cruzi*. They reported that the compound induced programmed cell death in both epimastigotes and trypomastigotes.

Rashid et al. (2014) tested fractions obtained from crude methanol extracts of aerial parts of *A. elegantissima* Pamp. and demonstrated that three fractions were active against *T. b. brucei*. In this study, two fractions were found to be active at concentrations of 10 and 20 μg/mL, while the remaining fraction was found to be active at all three concentrations tested namely 5, 10, and 20 μg/mL. During the study, 13 compounds were isolated, three of which were found to be active against *T. b. brucei*. The coumarin, scopoletin, was found to be the most active compound against *T. b. brucei* with minimum inhibitory concentration (MIC) of less than 0.19 μg/mL while the flavonoids bonanzin and 3,4-dihydroxy bonanzin also showed good antitrypanosomal activities. The authors concluded that the antitrypanosomal activity against *T. b. brucei* was primarily attributable to phenolic constituents. They further observed that the antiparasitic efficacy was significantly influenced by specific structural determinants, including molecular weight, the quantity of hydroxyl groups, and their substitution patterns on the flavonoid and coumarin scaffolds. In an *in vitro* activity study on *T. b. rhodesiense*, Dua et al. (2011) used leaves of *A. roxburghiana* Besser, cultivated in North-West Himalaya in India and demonstrated that the petroleum ether extract was active against *T. b. rhodesiense*. The extract exhibited good selectivity for *T. b. rhodesiense* with an IC_{50} value of 6 μg/mL. The extracts had also shown some antitrypanosomal activity against *T. cruzi*.

Ene et al. (2009) studied the antitrypanosomal activities of different extracts of *A. maciverae* on *T. b. brucei*. The petroleum ether, chloroform, and methanol extracts showed appreciable trypanosomal activity with the chloroform extract exhibiting the highest activity both *in vitro* and *in vivo*. The latter showed that the chloroform extract at a dose of 100 mg/kg in infected mice had the best trypanosomal activity, while a dose of 4 mg/kg caused complete cessation of *T. b. brucei* motility after 15 min. Further fractionation of the crude extract indicated that all fractions had antitrypanosomal activity *in vitro*, while a dose of 10 mg/kg body weight completely cleared parasitaemia in infected mice after treatment for 7 days. In another study, Ene et al. (2014) reported the *in vitro* and *in vivo* antitrypanosomal activity of *A. maritima* L. against *T. b. brucei* in Swiss albino mice. Using petroleum ether, chloroform and methanol extracts of the whole plant, it was demonstrated that all extracts were active against *T. b. brucei* with the petroleum ether extract showing the highest activity. Furthermore, the study identified the chloroform extract of *A. maritima* as the only fraction to demonstrate *in vivo* antitrypanosomal efficacy. Administered at a dosage of 100 mg/kg, this extract significantly curtailed the parasite load in *T. b. brucei*-infected mice, outperforming all other experimental groups. Specifically, treatment at this concentration resulted in a reduction of parasitemia levels to 26% of the control.

Awad et al. (2013) explored the antitrypanosomal efficacy of crude ethanolic extracts of *A. herba alba* against *T. evansi*. The findings revealed that subjects treated with crude ethanolic extracts of *A. herba alba* exhibited significantly reduced parasitemia and lower mortality rates in comparison to the negative control group. Molina-Garza et al. (2014) evaluated the activity of methanolic extracts of *A. mexicana* Spreng. against epimastigote forms of *T. cruzi in vitro*. The study reported an acceptable level of activity with an IC_{50} of 39.25 μg/mL. Da Silva et al. (2008) tested *A. vulgaris* extracts in *T. cruzi* infected mice and by using Technetium-99m diagnostic imaging reported that *A. vulgaris* significantly reduced parasitaemia.

3.6 Common *Artemisia* spp. lacking research

The genus *Artemisia* contains various species that are commonly found in (herb) gardens and can hence be obtained from nurseries. The Mountain Herb Estate Nursery (Kameeldrift, South Africa) lists ten *Artemisia* spp. four of which have already been discussed in this review (*A. afra*, *A. annua*, *A. absinthium* and *A. vulgaris*). The remaining species includes *A. abrotanum* L., *A. capillaris* Thunb., *A. arborescens* L., *A. dracunculus* L., *A. ludoviciana* Nutt., and *A. scoparia* Waldst. & Kit.. A literature search for any reports on these six common *Artemisia* spp. and their possible antitrypanosomal activity revealed that no research in this area has been conducted. However, there have been some reports from both conventional use and scientific studies against parasites in general that have indicated some promising effects; hence, future research may benefit from including these species to test for antitrypanosomal activity.

The Mountain Herb Estate Nursery describes the traditional, historically documented applications of the listed *Artemisia* spp. for both culinary and therapeutic purposes. For instance, *A. dracunculus*, often known as "Tarragon French," is a plant whose leaves and oil are used as an anthelmintic. It is regarded as a key ingredient in tartar sauce. The leaves and flower heads of Louisiana Wormwood (*A. ludoviciana*), a fragrant antimicrobial plant, are used to make tea, flavouring in sauces, game and pork meat and to treat sore throats. Feverish ailments are treated with *A. capillaris*, while intestinal parasites are treated with *A. vulgaris* (mugwort) and it is also used as an insect repellent. Elsewhere, *A. dracunculus* has been used to treat fevers and has been shown to be effective against leishmaniasis, which is related to *Trypanosoma* (Obolskiy et al., 2011). Yousaf et al. (2019) also reported antileishmanial activity of

Table 2: Antitrypanosomal activity of isolated compounds from *Artemisia* species.

Source	Compound	*Trypanosoma* spp.	Antitrypanosomal activity	Reference
A. annua	1,8-cineole	*T. b. brucei*	IC_{50} = 64.6 μg/mL	Efferth et al., 2011
A. annua	artemisinin	*T. b. brucei* & *T. cruzi*	IC_{50} = 24.4 μg/mL (*T. b. brucei*)	
			IC_{50} < 30.0 μg/mL (*T. cruzi*)	Bilia et al., 2008; Nibret and Wink, 2010
A. absinthium	trans-caryophyllene	*T. cruzi*	Concentration-dependent antitrypanosomal activity	Martínez-Díaz et al., 2015
A. elegantissima & *A. annua*	scopoletin	*T. b. brucei*	MIC = 0.19 μg/mL	Rashid et al., 2014
A. elegantissima	3,4-dihydroxy bonanzin	*T. b. brucei*	MIC = 6.25 μg/mL	Rashid et al., 2014
A. elegantissima	bonanzin	*T. b. brucei*	MIC = 20 μg/mL	Rashid et al., 2014
A. douglasiana	dehydroleucodine	*T. cruzi*	Programmed cell death	Jimenez et al., 2014
A. sieversiana	chrysosplenetin	*T. cruzi*	IC_{50} = 2.9 μM	Nurbek et al., 2020

different extracts of *A. scoparia* callus cultures against *Leishmania tropica* promastigotes. Baldemir et al. (2018) reported *A. ludoviciana* EO activity against *Leishmania infantum*, *Acanthamoeba castellanii* and *Trichomonas vaginalis*. Cubukcu et al. (1990) also conducted an *in vitro* study and demonstrated the antimalarial activity of two compounds derived from an ethanolic extract of *A. abrotanum*. Silver nanoparticles containing *A. arborescens* and *A. abrotanum* have also been shown to have antimalarial activity (Avitabile et al., 2020). In conclusion, some interesting antiparasitic scientific research has been conducted on these commonly found *Artemisia* spp. and future research endeavours on these spp. may yield interesting new lead compounds active against *Trypanosoma*.

4. Selected isolated compounds from *Artemisia* spp. with antitrypanosomal activity

A number of compounds with moderate to significant antitrypanosomal activity have been isolated from the genus *Artemisia*. Table 2 summarises some of the reported active compounds.

5. Conclusions and future perspectives

Current chemotherapies for the treatment of HAT and CD have serious drawbacks, such as long treatment periods with frequent treatment failures and varying degrees of toxicity, and emerging drug resistance is a growing problem. Natural products are a promising treatment option for these neglected tropical diseases, as well as a potential source of drug leads that follow different mechanisms of action. Lead compounds identified may be optimised by semi-synthetic derivatization where necessary for further drug development. Artemisinin exhibited lower trypanocidal activities compared to the acetone and n-hexane extracts of *A. annua* which were also shown not to contain the highest amounts of artemisinin (Bilia et al. 2008). Nibret and Wink (2010) also demonstrated that the DCM extract of *A. afra*, *A. absinthium* and *A. abyssinica* were more active than artemisinin or the corresponding *A. annua* extract. These findings suggest that the contribution of artemisinin to the observed antitrypanosomal activity—whether through direct action or synergistic interaction—is relatively minor. Consequently, other bioactive phytochemicals present within these and various other *Artemisia* spp. represent promising candidates for further investigation.

The *in vivo* study by Feyera et al. (2014) confirms their earlier *in vitro* studies (Feyera et al., 2011) on bloodstream forms of *T. congolense* using DCM extracts of *A. abyssinica*. The two studies also confirmed the earlier *in vitro* work by Nibret and Wink (2010) involving the activities of the lipophilic extract of *A. annua*, *A. absinthium*, *A. afra* and *A. abyssinica* on bloodstream forms of *T. b. brucei*. It is evident, therefore, that when different solvent systems are used in extraction procedures the lipophilic extracts exhibit the highest trypanosomal potential with fairly moderate cytotoxicity towards mammalian cells both *in vitro* and *in vivo* (Bilia et al., 2008; Ene et al., 2009, 2014; Malebo et al., 2009; Nibret et al., 2010; Dua et al., 2011; Efferth and Koch, 2011; Feyera et al., 2011, 2014; Mokoka et al., 2011; Bailen et al., 2013; Martínez-Díaz et al., 2015). This makes them a preferred extraction solvent and potential source of novel compounds in the search for alternative treatment options for tropical diseases.

Studies have also shown that isolated compounds have lower inhibitory activities compared to their parent plant extracts or fractions (Bilia et al., 2008; Nibret and Wink, 2010; Rashid et al., 2014; Martínez-Díaz et al., 2015;). While few attempts have been made towards isolating the active compounds, many are calling for further studies in order to achieve this (Bailen et al., 2013; Martínez-Díaz et al., 2015; Nass and Efferth, 2018). This further strengthens the argument regarding the presence of other bioactive phytochemicals or compounds having significant synergistic effects with active compounds. Indeed, further studies are needed to identify the compounds responsible for these remarkable antiparasitic effects. The studies, in our view, must include species where previous studies have demonstrated trypanosomal activities such as *A. annua*, *A. afra*, *A. absinthium* and *A. vulgaris* with a focus on isolating novel compounds responsible for the reported activities, but must also include other species with reported traditional use such as *A. abrotanum*, *A. capillaris*, *A. arborescens*, *A. dracun-*

culus, *A. ludoviciana*, and *A. scoparia* in the quest to find novel effective treatment options for trypanosomiasis.

CRediT authorship contribution statement

I. Mwila: Conceptualization, investigation, data curation, writing – original draft, visualization. D.D. N'Da: Writing – review & editing, supervision. F. van der Kooy: Conceptualization, resources, writing – review & editing, supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors have not used AI or AI-assisted technologies in the preparation of this manuscript.

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Data availability

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

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