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Potential anti-trypanosomal plants against African animal trypanosmiasis

Solomon Assefa

Abstract
The genus Trypanosoma, which is a flagellated protozoan, causes trypanosomiasis. The disease can be occurred in human and animals in Africa and South America. African animal trypanosomiasis (AAT) has a multidimensional impact in Africa. Treatment of AAT is currently facing a number of problems including toxicity of trypanocidal drugs and development of resistance by the parasites. These limitations have prompted the search for alternative active substances (such as of natural origin). There are many plants indicated for their use against the disease. In different ethnobotanical studies conducted in Africa, large number plants have been reported. Some of these plants has been tested and confirmed for their anti-trypanosmal activity against different species of trypanosome using *in vivo* and *in vitro* method. Different literatures were surveyed on antitrypanosomal activity published after the year 2005.

Keywords: African trypanosomiasis, medicinal plants, trypanocidal, anti-trypanosomal

1. Introduction
Trypanosomiasisis a parasitic disease caused by flagellated protozoan belonging to the genus *Trypanosoma* (Abebe, 2005) [4], this genus causes potentially fatal human and animal trypanosomiasis in Africa (African trpanosomiasis) and South America (American trypanosomiasis) (Pascal *et al*., 2009; Lima *et al*., 2010) [75, 41]. African trypanosomes cause African Animal trypanosomiasis (AAT), a debilitating disease of domestic animals in the humid and sub-humid zones of Africa (Muhanguzi *et al*., 2015) [57].
AAT also called nagana in Zululand (Connor RJ, 1998) [20] is caused by different species of the genus Trypanosoma. *Trypanosoma vivax*, *Trypanosoma congolense* and to a lesser extent *Trypanosoma brucei brucei* are the main species responsible for AAT (D'Archivio *et al*., 2011) [21]. Cattles are the primary victim of trypanosomiasis in West and East Africa. Sometimes epidemics can also occur in other species: horses, goat, dog, sheep and camel (Emma, 2008) [23]. Surra in camels and Dourine in horses are caused by the other trypanosome species of T*rypanosoma evansi* and T*rypanosoma equiperdum*, respectively (D'Archivio *et al*., 2011) [21].
The disease is majorly transmitted through the bite of tsetse fly (Glossina species) which introduces the causative agent, trypanosome, into the blood (WHO, 2003; D'Archivio *et al*., 2011) [96, 21]. The tsetse belt extends from Sahara in the North to South Africa in the South (OIE, 2013) [69]. Large areas of Africa, approximately 4 million km^2, have been rendered unsuitable for livestock production by trypanosomes (Emma, 2008) [23]. This makes AAT to be one of the vector-borne parasitic diseases which are causing major health and economic problems in rural sub-Saharan Africa (Molyneux, 1997) [54].
The impacts of AAT are multidimensional. The disease affects human health, livestock production, agricultural production, rural socio-economic development, national economies (import and export of animal products), and the environment (insecticide applications) (Abd-Alla *et al*., 2013) [1].
Trypanosoma is furthermore known to render approximately a quarter of African arable land mass unsuitable for profitable livestock farming (Molyneux, 1997) [54]. Hence, it causes the death of 3 million cattle annually with an estimated lost potential of $ 6-12 billion US dollars (Maikai, 2010) [46].
Commonly employed control methods of trypanosomiasis are chemotherapy and control of tsetse fly vectors (Magez *et al*., 2010) [43]. Accordingly, Programmes are under way to free Africa of the disease either by massive control and eradication of the tsetse fly (Abd-Alla *et al*., 2013) [1]. Vaccination is also considered to be one of the best methods of controlling infections. However, continuous antigenic variation and memory-cell destruction by trypanosomes limited the development of viable vaccines (Magez *et al*., 2010) [43].

The problem of drug resistance in trypanosomes chemotherapy appears to be spreading geographically to different regions, in which trypanosomiasis occurs. So far, resistance to one or more of the three trypanocidal drugs(Homidium, Diminazene, Isometamidium) used in cattle has been reported in at least 11 countries in sub-Saharan Africa(Burkina Faso, Chad, Côte d'Ivoire, Ethiopia, Kenya, Nigeria, Somalia, Sudan, Tanzania, Uganda, and Zimbabwe) (Afewerk *et al*., 2000; Melaku and Birasa, 2013; Chitanga *et al*., 2011) [9, 51, 19]. Moreover, Current treatments of animal trypanosomiasis possess several limitations, such as limited efficacy as well as severe side effects due to toxicity, including mortality (Onyekwelu, 1999; Faria *et al*., 2014) [72, 26].

Due to the above obstacles of chemotherapy, trypanosomiasis therapy urgently necessitated the development of alternative new molecules that are safe, effective and affordable. In this respect, different literature surveys and field studies have shown that plants are used in traditional medicine of Africa to treat trypanosomes in humans and animals (Freiburghaus *et al*., 1996; Nibret and Wink, 2011) [29, 60, 63, 65].

At least 80% of the world population is estimated to be employing traditional medicines that commonly use natural products in primary health care (Verpoorte *et al*., 2006) [93]. Plants, animals and micro-organisms represent a reservoir of natural products, the so called "natural sources deriving compounds" (Brusotti *et al.,* 2011) [18]. Plants are the major component of traditional medicine, including 40,000-70,000 medicinal plants, out of which 20% of them are higher-plant species (Verpoorte*et al*., 2006) [93]. In an effort to discover new lead compounds for infectious diseases, researchers are focusing on plant materials which contain array of diverse chemical substances with biological and physiological properties (Maikai, 2010) [46]. Developing drugs from natural products created a consensus among the scientific community (Newman *et al*., 2003). Hence, this review tries to overview medicinal plants that are promising to develop anti-trypanosomial agents, particularly used in African trypanosomiasis.

PubMed, Sciencedirect, Medline and Google scholar were used for searching of the relevant literatures published after 2005 that dictates about medicinal plants used in the management of AAT. Certain articles were found through tracking citations from other publications. The keywords combinations for the search were: anti-trypanosomal, trypanocidal, medicinal plant and Africatrypanosmiasis. The research articles obtained on the ethonobotanical study and in vitro and in vivo antitrypanosomal activities are presented in this review.

Plants used in traditional medicine against African Animal Trypanosomiasis

With different attempts made in the past thirty years, failures in control measures and treatment regimes have caused the impact of this parasite to increase markedly (WHO, 2003) [96]. In poor countries, the healthcare is often sustained by practices based on cultural alternatives (Willcox and Bodeker, 2004) [94]. It has also been observed that natural products derived from plants offer novel possibilities to obtain new drugs that are active against trypanosomes. Many investigators targeted finding new anti-trypanosomal agents to combat the trypanosomomiasis by screening extracts of medicinal plants (Mann and Ogbadoyi, 2012) [48]. There are many reports about the screening of herbal extracts against *T. brucei brucei*, *T. congolense* (Kayser *et al*., 2003) [37] and *T. evansi* (Kumar *et al*., 2014) [40]. However, these investigations are in their infant stages. These review compile and present a recent information on various plant used against AAT.

Maikai, *et al.* (2010) [46] in their ethnobotanical study has reported that *Khaya senegalensis* (23.3%) had the highest percentage of traditional use against AAT followed by *Terminalia Avicennioides* (16.3%), *Ximenia Americana* (12.7%), *Anona senegalensis* (10.7%) and *Azadirachta indica* (9.3%) in Kaduna State, Nigeria. The authors also added that the leaves, bark and roots were the main parts of the plant used traditionally. Besides the above plants, The leaves of *Guiera senegalensis*, leaves of *Tamarindus indica* and bark of *Prosopis africana* has also been stated to be used in the traditional medicine of Nigeria (Maikai *et al*., 2010) [46].

In other regions of Nigeria called *Lavun* local Government area of Niger State, Mann and Ogbadoyi (2012) [48] collected plants based on the description made by the traditional healers for their use in AAT traditionally. The plant materials used traditionally include: *Acacia nilotica* (stem bark), *Bombax buonopozense* (stem bark), *Heterotisrotun difolia* (whole plant), *Pterocarpus erinaceus* (stem bark), *T. avicennioides* (round fruit), and *Zanthoxylum zanthoxyloides* (stem bark).

Maikai *et al.* (2010) [46] also reported that *Terminalia brownii, Acacia refiscens, Clarodendrum species, Afzelia africana, Cordia myxa, Eugenia uniflora, Acacia artaxacantha, Terminalia uorensis* and *Strophanthus sarmentosus* are used in Kenya, Nigeria and other countries by herdsmen to locally treat their animals.

Salihu *et al* (2014) [77] has interviewed 64 Fulani herdsmen in Taraba, Nigeria, and they reported that *K. senegalensis* was the most frequently (20.93%) used anti-trypanosomal plant. In addition, *A. senegalensis* and *Prosopsis africana* were used by some of the herdsmen. The common plant parts used as remedies by the Fulani herdsmen interviewed were leaves, stem and root. As it is indicated earlier (Makai *et al*., 2010) *K. sengalensis* is also found to be the major plant against the disease in other part of Nigeria (*Kaduna*)

Several plant species have been used to treat trypanosomiasis in East Africa. These include *Adenia volkensii*, *Fagara chalybea* and *Salvadora persica*, which are used in Kenya (Ole-Miaron, 2003).

In the first stage, plant extracts are evaluated *in vitro* against bloodstream forms (Kayser *et al* 2003) [37]. These plants are also investigated in animal models, which are infected with trypanosome parasite. Accordingly, those plants reported to be used in traditional medicine has been investigated for their *in vitro*/*in vivo* anti-trypanosomial activity; the following are some of them.

Plants evaluated for their anti-African trypanosomal activity

Plant extracts have been extensively screened for their antitrypanosomal activity in the recent years and some have shown promising anti-trypanosomal potential (Habila *et al*., 2011; Nwodo *et al*., 2015) [33, 67].

Atowadi (2005) has tested about forty tropical plants harvested from the savannah against *T. brucei brucei*. Among the plants studied, extracts of *Adenium obesum* (stem bark), *Afrormosia laxiflora* (leaves and stem bark), *Cochlospermum planchonii* (stem bark), *P. africana* (stem and root barks), *Striga spp* (leaves), *T. avicennioides* (root and stem bark) and *Swartzia madagascariensis* (fruit pulp) exhibited the highest trypanocidal activity. These results suggested that tropical plants could be a very promising source of new generations of trypanocidal agents.

In the *In vitro* anti-trypanosomal study, the crude extract of *Ocimum gratissimum* Linn that is used in folk medicine of Benin were found to be more active than its essential oils and their major compounds against *T.brucei brucei*. The most active extracts were obtained from seeds and leaves in full flowering stage (IC_{50}<2 mg/ml) (Bénédicta *et al*., 2014) [15].

In study conducted by Awobode *et al* (2015) [13], the antitrypanosomal activity of combined methanolic stem bark extracts of *K. senegalensis* and *A. leiocarpus* were determined in vivo using suppressive and repository tests. The combined extracts were administered at 250 mg/kg to *T. brucei brucei* infected rats in ratios 1:4, 2:3, 1:1, 3:2 and 4:1 (*K. senegalensis* to *A. leiocarpus*). Trypanocidal activity was recorded in all four ratios with the highest being in the 4:1 ratio for both tests. All ratios in repository test had varying levels of prophylactic activity which were significantly higher ($p<0.05$) than the negative control group. Chemo-prophylactic activity in the 4:1 ratio compared favorably with the positive control.

K. senegalensis root bark was extracted with methanol and screened against *T. evansi* for *in vitro* trypanocidal activity. At 250 µg/ml, there was immobilization, reduction of average trypanosomes counts and complete killing of trypanosomes at 6 h of incubation, which was equivalent to diminazene aceturate 50 µg/ml at 4 h (Shaba *et al*., 2011).

At 250 µg/ml, trypanocidal activity of methanolic extract of *K. senegalensis* tree bark at 6 h of incubation is equivalent to 4 h of diminazine aceturate (standard drug). The study indicated the potency of methanolic extract of *K. senegalensis* in comparison to pure compound of diminazene aceturate (Shaba *et al*., 2011).

Aqueous and methanol extracts of different parts of *A. leiocarpus* were analyzed for in vitro antitrypanosomal activity against *T. brucei brucei*. Extracts of the different parts of the plant were found to possess *in vitro* antitrypanosomal activity against *T. brucei brucei*. Different parts of the plant showed variations in their anti-trypanosomal activity. Methanolic and aqueous extracts of the plant bark had the highest *in vitro* activity against the parasite (Wurochekke and Anyanwu, 2012) [98].

The *in vitro* effect of *A. leiocarpus* was evaluated by other researchers. Their reports showed that the active butanolic fractions and the isolated compounds exhibited minimum inhibitory concentration (MIC) values ranging from 25 to 50 µg/ml and 7.5 to 31.5 µg/ml, respectively, against *T. evansi.* This confirmed the activity of the plant against *T. evansi* in addition to the above showed activity against *T. brucei brucei* (Shuaibu *et al*., 2008) [83].

Antia *et al* (2009) [11] has reported the result obtained from the anit-trypanosomial activity of some medicinal plants from Nigeria. It was noted that the stem and root bark extracts of *Terminalia superba* caused complete cessation of motility of parasites at 3.1 mg/ml extract concentration. While the leaf extracts of the same plants only caused cessation at a higher concentration of 6.3 mg/ml. The root bark and leaf extracts of *A. Africana* also caused completed cessation of motility at 6.3 and 3.1 mg/ml respectively. *T. superba* root extract also exhibited appreciable activity *in vivo* in rats and mice used in their study.

Water, methanol and dichloromethane extracts of the leaves of *T. avicennioides* was tested, but only methanolic extracts were found to be active against *T. Brucei brucei*. In addition, the round fruit extract of *T. avicennioides* tested for its *in vivo* antitrypanosomal activity and gave a good anti-trypanosomal result (Mann and Ogbadoyi, 2012) [48]. This finding was similar to other study done on the activity of this plant (Bizimana *et al*., 2006) [17] in which statistically significant ($p=0.002$) reduction of parasitemia was observed compared to the negative control. Mann and Ogbadoyi (2012) [48] also investigated the anti-trypanosomal activity of Stem bark of *Z. zanthoxyloides,* and it was found to exhibit trypanostatic activity.

At doses of 10, 20 and 40 mg/kg, the crude extract *Abrus precatorius* seeds showed a sharp reduction in the level of parasitemia in mice compared with untreated group against resistant strain of *T. brucei brucei.* In addition, one of the fractions, which contained mainly alkaloids, was screened for its pharmacological activity. This fraction at doses of 5 and 10 mg/Kg showed a sharp reduction in the level of parasitemia to zero in day 9 and gradual recovery from the 12th day of treatment. This effect of the fraction was found to be comparable to diminazene aceturate (Nwodo and Nwodo, 2012) [68].

Certain medicinal plants from central Africa have been reported to exhibit activities *in vitro*; including *Garcinia lucida* (Fotie *et al*., 2007) [56]. The stem bark crude extract of *G. lucida* displayed significant activity against *T. brucei brucei* (IC_{50} =4.9 µg/mL) with no toxicity on the Vero cell. Moreover, the aqueous extract from *Isolona hexaloba* stem bark showed pronounced activity against *T. brucei brucei* (IC_{50} =1.95 µg/ml) while stem bark of *Enanatia chlorantha* has good anti-trypanosomal activity (IC_{50} = 8.36 µg/ml) (Muganza *et al*., 2012) [55].

Abedo *et al* (2013) [3] showed the activity of nine extracts recovered from plant materials of *Tapinanthus globiferus* and *G. latifolium* against *T. congolense in vitro* at various concentrations (2.5, 5 and 10mg/ml). The methanolic leaf extract of *T. globiferus* showed highest activity by ceasing the motility of the parasite within 5 minutes, followed by methanolic stem bark extract of *G.latifolium*, which ceased motility at 10 minutes. All the extract obtained from both plants was trypanocidal except the aqueous extracts of Leaf, stem bark of *G. latifolium* and stem bark *T. globeferus*.

Preliminary Screening of *X. americana* using stem bark extract has been done for anti-trypanosomal activity against blood stream forms, the results showed that methanol extract had *in vitro* activity against *T. congolense.* Aqueous and methanolic extracts reduced motility of the parasite in various concentrations (Maikai *et al*., 2008) [45].

According to Bero *et al* (2011), the best growth inhibitions of *T. brucei brucei* were observed with the Dichloromethane extracts of *Acanthospermum hispidum*, *Byrsocarpus coccineus*, *Carpolobia lutea*, and *Keetialeucantha* twigs with IC_{50} value of 14.5, 14.7, 18.3 and 5.8µg/ml, respectively. The methanol and water extracts of *Anchomanes difformis* has also exhibited IC_{50} value of 14.7 µg/ml against *T. brucei brucei*. In addition to these plants, the authors has tested *Pupatialapacea*, *Samseveria libericia, schrankia leptocarpa* for their anti-trypanosmoal activity based on their traditional claim in Benin, but they did not show any strong antiparasitic activity (Bero *et al*., 2011).

50 mg/kg Cold water whole plant extract of *Peristrophebicalyculata* immobilized 90% of the parasites after 60 min of incubation, and its solvent fraction 2c completely immobilized the parasites after 35 min. It significantly increased packed cell volume (PCV) in *T. brucei brucei*infected rats (Abimbola *et al*., 2013) [5].

In 2009 Adeiza *et al* has tested the *in vitro* trypanocidal activity of *A. senegalensis* and found that the crude extract immobilized *T. evansi* at 10 mg/ml. The same year Adeyemi

et al (2009) [7] reported the results obtained from treatment with ethanolic extract of *P. guajava* which leaf indicated the leaf extract could be effective in the management of AAT, since *P. guajava* has trypanocidal properties as well as the ability to extend the life span of T. brucei-infected rats.

Alhaji *et al* (2014) [10] evaluated the *in vitro* anti-trypanosomal activity of the aqueous extracts of nine Nigerian medicinal plants. From their study, it was discovered that the stem bark extracts of *Acacia albida* and *Pericopsis laxiflora* were most active against both *T. evansi* and *T. congolense*. There was complete cessation of motility in both trypanosomes within 5 min at 40 mg/mL of the stem bark extract of *A. albida*. Complete cessation of motility was observed within 25 min and 40 min at 40 mg/ ml with *P. laxiflora* stem bark extract for *T. congolense* and *T. evansi*, respectively.

Table 1 summarizes other plants reported to have pharmacological activity against African trypansomiasis either in vivo or in vitro against different species of the African trypanosoma.

Ethiopian plants claimed against AAT

In Ethiopia, a substantial amount of the national resource is spent annually for the control of trypanosomiasis (Tikubet, 2000) [91], which is also known as *gendi* locally (Gidey and Ameni, 2003) [31]. Modern veterinary medicines are not well developed in Ethiopia, nor are modern drugs available adequately to fight animal diseases (Ketema *et al*., 2013) [38]. In the country about 90% of livestock depends on traditional herbal medicine for treatment of various ailments (Birhan *et al*., 2011) [16].

According to the ethnopharmacological study done by Tekle (2014) [87], 4 plants were found to be used in the traditional medicine for the treatment of AAT in *kochere* district of southern Ethiopia. The plants named *Viginia* spp. (Kellea), which belongs to Fabeaceas family leaves is used for the treatment of the disease. Moreover, The root, bark and leaves of *Zeheneria scabra* lin. (keite), *Erythena brucei* (gliena), *Irseine herbstili*, respectively is reported to have traditional use in the management of the disease in Gedeo zone (Tekle, 2014) [87].

In afar, *Balanties aegyptiaga* root also known as *uda* is indicated for the management of camel trypanosmiasis (locally termed *geremole*) (Gidey and Teklehaymanot, 2013) [32]. *Clutia abbysinica* plant has been reported to have several medicinal uses in the treatment of infectious disease including trypanosomiasis, in Dek highlands (Teklehaymanot, 2009) [89] and other areas of Ethiopia (Fullas, 2010) [30].

Allium cepa (qey shiknurt), *phytolacca dodencandra* (arenji), *Rumex nepahlesis* (yewsha tej), *Verbas cumstintacum* (kutina) (Woldegerima *et al*., 2008) [97], and *Clausena anisata* (limch) (Fullas, 2010) [30] has been also reported to be utilized as a traditional remedy of AAT in different part of the country.

In Jimma zone, Ethiopia, leaves of *Ocimum lamiifolium* Benth.(Lamiaceae) and *croton macrostachys* (euphorbiaceae) also locally known as, Damakase and Bisana, respectively are pounded and extract is given to cattle (2 teaspoons/dose) administered nasally. The other traditional remedy for AAT in the zone is plant *Verbascum sinaiticum* (Yigezu *et al* 2014) [102]. *V. sinaiticum* has been also stated in other reports to have anti-trypanosomal use in other part of the nation (Woldegerima *et al*., 2008) [97].

Tadesse *et al* (2014) [84] has reported about the traditional use of *A. indica* (Meliaceae) in the management of AAT in East Wollega Zone, Western Ethiopia. In trypanosomiasis, the leaf of the plant is administered orally.

Root of *Solanum anguivi* Lam.(Solanaceae) is mixed with water and given One bottle for three days in the treatment of AAT, in Wayu Tuka District, East Welega Zone of Oromia Regional State, West Ethiopia (Megersa *et al.,* 2013) [50].

A total of 18 types of medicinal plants have been reported to be used in control and prevention of trypanosmomiasis by Shilema *et al* (2013) [64]. 7 (38.9 %) of the medicinal plants were indicated for AAT treatment, 4 (22.2%) as a tsetse fly repellant and 7 (38.9 %) for both AAT treatment and tsetse fly repellant. *Lepidium sativum* L. (Sibaka), *Echinops Kebericho* (Boruse), *Allium sativum* (Tuma), *Withania somnifera* (Tiro), and *Myrica salicifolia* (Bundo) are the five most common plant species for the treatment of animal trypanosomiasis respectively as indicated by the respondents in Amaro district in southern Ethiopia (Shilema *et al*., 2013) [64].

In other area of southern Ethiopia (Bensa woreda) different plants were reported to be used in traditional veterinary medicine. Among these plants, leaves of *Clerodendrum myricoides* (Malasincho), *Ranunculus glandulosus* (Qenta/qinta), and *Plectranthus multifidus* are used in the treatment of AAT (Tekle, 2015) [88].

In Ethiopia, modern investigation on herbal remedies for human ailments has been going on for a while. On the other hand, similar efforts in the area of research on plant remedies for livestock diseases seem to be lagging behind (Fullas, 2010) [30]. Therefore scientific evaluation of these plants may provide modern medicine with lead compounds for the development of new drugs. Some of the plants have been evaluated for their pharmacological activity.

Ethiopian plants authenticated for their anti-trypanosomal activity

Trypanocidal effects of dichloromethane and methanol extracts of traditionally used 30 Ethiopian medicinal plants species were evaluated on bloodstream forms of *T. b. brucei*. Of all, dichloromethane extracts from five plants showed better trypanocidal activity, including: *Dovyalis abyssinica (Flacourtiaceae), Albizia schimperiana (Fabaceae), Ocimum urticifolium (Lamiaceae), Acokanthera schimperi (Apocynaceae),* and *Chenopodium ambrosioides (Chenopodiaceae),* with IC50 of 1.4, 7.2, 14.0, 16.6 and 17.1 µg/ml, respectively. The researchers speculated that *D. abyssinica* might be a promising candidate for phytotherapy of trypanosomiasis (Nibret and Wink, 2011) [60, 63, 65]. Some of these plants have been tested for their in vivo activity (Tadesse *et al*., 2015, Tesfaye *et al*., 2015) [85, 86].

Nibret *et al* (2009) [59] determined the in-vitro effect of extracts from 19 Ethiopian plant species and four pure pyrrolizidine alkaloids on bloodstream forms of *T. brucei brucei*. The dichloromethane extract of *Solanecio angulatus* flowers was the most active extract against *T. brucei brucei*, with an IC_{50} value of 12.17 µg/ml. The other active extracts were the crude dichloromethane extracts of *Crotalaria phillipsiae* twigs (IC_{50} = 12.67 mg/ml) and *Solanecio manni* leaves (IC_{50} = 24.89 mg/ml). Among the four pure pyrrolizidine alkaloids tested, senecionine showed moderate antitrypanosomal activity with an IC_{50} value of 41.78 µg/ml. the authors suggested that *Solanecio angulatus* (flowers) and *Crotalaria phillipsiae* (twigs) could serve as sources of novel trypanocidal compounds for the treatment of trypanosomiasis (Nibret *et al*., 2009) [59].

A report on volatile components of four Ethiopian *Artemisia* spp. extract and their *in vitro* anti trypanosomal and cytotoxic activities, is a published in phytomedicne by Nibret and Wink (2010a) [61]. According to the study, Artemisia species are one

of the many traditional medicinal plants of Ethiopia used for the treatment of infectious and non-infectious health problems. Eight extracts prepared from leaves and aerial parts of four Artemisia species (*Artemisia absinthium*, *Artemisia abyssinica*, *Artemisia afra*, and *Artemisia annua*) growing in Ethiopia were tested and confirmed to have in vitro anti-trypanosomal activity against bloodstream forms of *T. brucei brucei* (Nibret and Wink 2010a) [61]. Artemisinin, the best known antimalarial compound from *A. annua* showed antitrypanosomal activity with an IC_{50} value of 35.91 µg/ml (Nibret and Wink 2010a) [61].

Essential oils from three Ethiopian medicinal plants; *Hagenia abyssinica* (Rosaceae), *Leonotis ocymifolia* (Lamiaceae), and *Moringa stenopetala* (Moringaceae) were investigated for their *in vitro* trypanocidal (*T. brucei brucei*) by Nibret and Wink (2010b) [62]. The oil of *M. stenopetala* seeds and its main compound, benzyl isothiocyanate showed the most potent trypanocidal activities with IC_{50} values of 5.03 µg/ml and 1.20 µg/ml, respectively. The oils of *H. abyssinica* and *L. ocymifolia* exhibited trypanocidal activities with IC_{50} values of 42.30 µg/ml and 15.41 µg/ml, respectively.

Feyera and his colleagues (2011, 2014) [27, 28] reported on the anti-trypanosomal activity of crude DCM and methanol aerial part extracts of *A. abyssinica*. According to their findings, both plant extracts showed appreciable *in vitro* and *in vivo* antitrypanosomal property against field isolate of *T. congolense* in mice. With the dichloromethane extract exhibiting the higher activity. It was reported that after incubation with the dichloromethane extract, trypanosome motility was eliminated by either completely immobilizing or killing the parasites within 18 and 40 min, respectively, at 4 mg/ml and 2 mg/ml concentration levels. This finding in part confirms an earlier in vitro work by Nibret and Wink (2010a) [61] involving the plant, and using the same solvent of extraction but against a drug sensitive *T. brucei brucei.*

Very recently, Among the 30 medicinal plants tested for their anti-trypanosomal activity against *T. b*rucei *brucei* by Nibret and Wink (2011) [60, 63, 65], the one with higher anti-trypanosmal activity (*D. abyssinica*) *in vitro* has been investigated for its *in vivo* activity against *T. congolense* by Tadesse *et al* (2015) [85].

According to Tadesse *et al* (2015) [85], Administration of higher curative doses (250 and 200 mg/kg) of DCM and methanol extracts of the plant considerably displayed *in vivo* activity as evidenced by reduction in parasitemia level despite the failure to completely clear bloodstream form of the parasite. The study confirmed for the presence of spermidine alkaloids in *D. abyssinica* that may in part account for the observed anti-trypanosomal activity of this plant. Other Ethiopian plants with proven anti-trypanosomal activity are listed in table 1

Table 1: Plants confirmed to have anti-trypanosomal activty against African Animal trypanosomiasis

Plant	Trypanosoma	Part used	References
Picrorhiza kurroa	*T. evansi*	Rhizomes	Shaba *et al*.,2012
Quercus borealis	*T. evansi*	Leaves	Shaba *et al*.,2011a
Zingiber officinale	*T. evansi*	Roots	Shaba *et al*.,2011a
Vitex negundo	*T. evansi*	Leaves	Shaba *et al*., 2008
Calotropis gigantea	*T. evansi*	Leaves	Shaba *et al*.,2011b
Camellia sinensis	*T. evansi*	Leaves	Shaba *et al*., 2011c
Morinda morindiodes	*T. brucei. brucei*	Root barks	Olukunle *et al*.,2010
Tithonia diversifolia	*T. brucei. brucei*	Leaves	Olukunle *et al*.,2010
Acalypha wilkesiana	*T. brucei. brucei*	Leaves	Olukunle *et al*.,2010
Acalypha Wilkesiana	*T. brucei. brucei*	leaves	Saleh *et al*., 2015
Argemone mexicana	*T. evansi*	Entire plant	Abdelrahman, 2011
Aristolochia bracteolata	*T. evansi*	Entire plant plant	Abdelrahman, 2011
Tinospora bakis	*T. evansi*	Entire plant	Abdelrahman, 2011
Artemisia myviverae	*T. brucei. brucei*	Whole plant	Ene *et al*., 2009
Heamastostaphis barteri	*T. evansi/ T. Congolense*	Stem bark	Wurochekke *et al*., 2014a
Goniothalamus umbrosus	*T. evansi*	Leaves	Dyary *et al*., 2014
Garcinia hombroniana	*T. evansi*	Leaves	Dyary *et al*., 2014
Strophanthus sarmentosus	*T. brucei. brucei*	stem	Onotu *et al*., 2014a
Lanneawel wistchii	*T. brucei. brucei*	root bark	Antia *et al 2009*
Punica granatum	*T. brucei. brucei*	leaf	Inabo and Fathuddin, 2011
Senna occidentalis	*T. brucei. brucei*	leaf	Mustapha *et al*., 2013
Lawsonia inermis	*T. brucei. brucei*	leaf	Wurochekke and Nok, 2004
Peristrophe bicalyculata	*T. evansi*	leaf	Awulu, *et al*., 2013
Cantharellus cibarius	*T. evansi*	Mushroom	Abedo *et al*., 2015
Carissa Spinarum	*T. brucei brucei*	Leaf Extract	Onotu *et al* 2014b
Moringa oleifera Lam	*T. brucei brucei*	Leaf	Igbo *et al*., 2015
Buchholzia coriacea	*T. congolense*	Seed	Nweze *et al*., 2011
Dissotis rotundifolia	*T. brucei. brucei*	leaf	Mann *et al*., 2009
Adansonia digitata	*T. Congolense*	Seed	Ibrahim *et al*, 2012
Combretum racemosum	*T. brucei. brucei*	leaf	Eze *et al*., 2012
Butyrospermum paradoxum	*T. congolense/ T. brucei. brucei*	stem bark	Mbaya *et al*., 2007
Aristolochia ringens	*T. congolense*	Leaves	Osho and Lajide, 2014
Carissa edulis	*T. Congolense*	Root, bark and Leaf	Wurochekke *et al*., 2014b
A. senegalensis	*T. brucei. brucei*	Stem Bark	Kabiru *et al*., 2010
Ceiba pentandra	*T. brucei brucei*	barks	Bizimana *et al*., 2006
Waltheria indica	*T. brucei brucei*	leaves	Madaki *et al*., 2016
Vernonia amygdalina	*T. brucei brucei*	leaves	Madaki *et al*., 2016

Albizia ferruginea	*T. brucei brucei*	leaves	Madaki *et al*., 2016
Camellia sinensis	*T. brucei brucei*	leaves	Madaki *et al*., 2016
Chamaecrista mimosoides	*T. brucei brucei*	leaves	Madaki *et al*., 2016
Hyptis suaveolens	*T. brucei brucei*	leaves	Madaki *et al*., 2016
Morinda lucida	*T. brucei brucei*	stem and leaves	Abubakar *et al*., 2016
Tridax procumbens	*T. brucei brucei*	stem and leaves	Abubakar *et al*., 2016
Camellia sinensis Salvia offiicinalis	*T. evansi*	leaves	Barghash, 2016
Thymus vulgaris	*T. evansi*	leaves	Barghash, 2016
Azadirachta indica	*T. evansi*	leaves	Barghash, 2016
Mentha longifolia	*T. evansi*	leaves	Barghash, 2016
Securidaca longipedunculata	*T. brucei brucei*	stem-bark	Tauheed *et al*, 2016
Azadirachta indica	*T. evansi*	seeds	Habila *et al*., 2011
Tetrapleura tetraptera	*T. brucei brucei*	fruit	Muganza *et al*., 2012
Hymenocardia acida	*T. brucei brucei*	stem bark	Abu and Uchendu, 2011
Aloe gilbertii	*T. congolense*	exudate	Tewabe *et al*.,2014
A. absinthium	*T. congolense*	leaves	Kifleyohannes *et al*., 2014
M. stenopetala	*T. congolense*	Aerial part	Kifleyohannes *et al*., 2014
C. abyssinica	*T. congolense*	leaf	Mergia *et al*., 2015
A. Schimperiana	*T. congolense*	Leaf	Tesfaye *et al*., 2015
Verbascum sinaiticum	*T. congolense*	leaf	Mergia *et al*., 2016

Conclusion

It is clear that medicinal plants play a prominent role against various human and animal diseases. A variety of medicinal plants and plants extracts have been reported for their significant anti-trypanosomal activity. This review represents an overview of the potentials of these plants in combating the disease. Different plants traditionally used for the management of African animal trypanosomiasis were evaluated in *in vitro* and *in vivo* study. Mode of action of the plants or their active ingredient is almost not studied in detail. The review concluded that flora is a potential suitable initial point to discover new and efficacious trypanocidal drug.

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