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In Vivo and *In Vitro* Antitrypanosomal Activities of Nigerian Medicinal Plants

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Abstract- African trypanosomiasis is one of the neglected tropical diseases caused by different species of trypanosomes that affect both human and livestock with devastating consequences in the continent. Clinically available chemotherapeutic drugs have been reported to be ineffective and also have severe side-effects. Plants have been used for many centuries with the purpose of feeding populations worldwide and to establish or bring back health, well-being, and the cure for several illnesses. A vast majority of people from less developed countries, including Nigeria depend on medicinal plants for the treatment of various diseases, due to the high cost of synthetic drugs. The present review reported the *in vivo* and *in vitro* antitrypanosomal activity of Nigerian medicinal plants. Almost seventy medicinal plants were reported for antitrypanosomal activity in this paper. The paper recommended that further research on other medicinal plants should be investigated for antitrypanosomal activities.

***Keywords*:** *In vivo*, *in vitro*, Extract**,** plants, trypanosomes

I. INTRODUCTION

Human African trypanosomiasis (HAT) or sleeping sickness is a severe fly-borne disease caused by protozoan of the species *Trypanosoma brucei* (T.b.) [1,2]. HAT occurs in two forms: the Gambian or West African form caused by T.b. *gambiense* and the Rhodesian or East African form caused by T.b. *rhodesiense* [2]. Most important species responsible for the disease complex, commonly known as Nagana, surra and souma in livestock include *Trypansoma brucei, T. congolense, T. evansi* and *T. vivax while T. gambiense, T. rhodesiense* and *T. cruzi* are important human pathogens responsible for sleeping sickness [3]. African trypanosomiasis is one of the neglected tropical diseases caused by different species of trypanosomes that affect both human and livestock with devastating consequences in the continent [4]. It is a major cause of death in sub-Saharan Africa and poses a major health and economic burden in these regions with an estimated 60 million people at risk of contracting this disease, which is fatal if left untreated [1]. Atawodi [5] noted that the significance of trypanosomosis to human health, nutrition and economy is enormous, thereby necessitating continuous research for better ways of eliminating the disease. Reference [4,6,7] reported that prevalence of the disease is strongly dependent on control measures, which are often neglected during periods of political instability leading to resurgence and on the other hand, the hope for vaccine development against the infection is still elusive.

Current chemotherapies of HAT are directed either to the early or late stages of the disease. All the clinically available HAT chemotherapeutic drugs have been noted to be ineffective, and they also have severe side-effects. The only drug candidate in clinical trials for the treatment of HAT is the nitroimidazole fexinidazole. Fexinidazole is currently in clinical study for the treatment of the late stage form of HAT [8,9]. The search for alternative compounds against African trypanosomiasis is justified by various limitations of existing chemotherapeutic agents [10]. A vast majority of people from less developed countries, including Nigeria depend on medicinal plants for the treatment of various diseases, due to the high cost of synthetic drugs [11]. Most of these plants have proved to be useful sources of treatment of various diseases. Lack of cost effective drugs is a major drawback in the treatment of trypanosomiasis. Most of the anti-trypanosomal drugs currently available in market are either highly toxic to animal or the parasites rapidly becomes resistant to these drugs [11,12]. This review aims to provide updated information of various medicinal plants use in the treatment of trypanosomiasis in Nigeria.

II. MEDICINAL PLANTS IN USE

Plants have been used for many centuries with the purpose of feeding populations worldwide and to establish or bring back health, well-being, and the cure for several illnesses [1]. Plants synthesize a large number of organic compounds also called primary metabolites that contribute to the production of carbohydrates, lipids, and proteins, among others, that are necessary for their growth. They also generate a small amount of a variety of secondary metabolites known as phytochemicals that are represented by alkaloids, carotenoids, flavonoids, saponins, hydroxycinnamic acids, and triterpenoids, among others [13]. Plants have provided the basis for traditional treatment for different types of diseases and still offer an enormous potential source of new chemotherapeutic agents [3]. Plants present a spectrum of biological compounds with activities against virus, cancer and parasites.

Nigeria is naturally blessed with both savannah and tropical rainforests vegetation and these offer a wide spectrum of unique medicinal plants [14,15]. Medicinal plant species constitute a valuable alternative to conventional medicine in many developing countries; especially in poor communities that inhabit rural areas, lacking access to health services. Several of them use plants as the primary health care, as teas, plasters, infusions, and ointments among others. The traditional use of medicinal plants and natural remedies with no established efficacy and safety is a widespread in many countries around the world [1]. The use of medicinal plants is very advantageous in terms of resource on chemical and biological research in natural products area. The plant secondary metabolism yields a wide range of chemical compounds, most of them highly bioactive and whose structural diversity is continuously evolving together with plants [1]. In this way, many classes of secondary metabolites, pure compounds, and its derivatives have been specifically tested *In vitro* and *In vivo* assays to verify their trypanocidal efficacy [1].

III. IN VITRO AND IN VIVO ANTITRYPANOSOMAL ACTIVITIES

Several researches were conducted by individual or group of researchers in order to investigate the antitrypanosomal activities of plants grown up and harvested in Nigeria. This paper report the following:

Wurochekke and Nok [16] investigated the *in vitro* trypanocidal activity of 13 medicinal plants used by local herdsmen in Northern Nigeria for the treatment of trypanosomosis. The plants includes; *Vernonia amygdalina, Khaya senegalensis, Balanites aegyptiaca, Lawsonia inermis, Tamarindus indica, Cassia siamaelam, Albezia Lebeck, Maytenus Senegalensis, Guira senegalensis, Ziziphus abyssinica, Ziziphus spinachristi, Xeminia ameriana,* and *Cassia sieberiana.* Forty-four different extracts prepared from the 13 plants were screened for *in vitro* activity against *T. b. brucei.* Four of the extracts showed activity against the parasite at minimum concentration of 8.3 mg/ml of blood. The *In vitro* antitrypanosomal activity of methanolic extracts of *Anogeissus leiocarpus* and *Terminalia avicennioides* against four strains of Trypanosoma species with minimum inhibitory concentration (MIC) value range of 12.5–50 mg/ml were evaluated [17]. Successive fractionations of the two plant extracts in water, butanol and ethyl acetate gave a range of activity (MIC, 20 to ≥50 μg/ml). Activity-guided and chromatographic analysis of butanolic fractions on Sephadex LH-20 column followed by high-performance liquid chromatography, nuclear magnetic resonance analysis and both ultraviolet and thin layer chromatography revealed hydrolysable tannins with a range of activity (MIC, 7.5–27.5 μg/ml or 14–91 μM). Effect of the compounds on fibroblasts did not reveal serious toxicity at moderate concentration but is concentration dependent.

The relative antitrypanosomal and haemolytic activities of the methanol extracts of 10 Nigerian medicinal plants extracts including the leaf, stem bark and root bark of *Afzelia africana, Khaya senegalensis* and *Terminalia superb*a as well as the leaf extract of *Lannea welwi*stchii were investigated [18]. All the extracts showed varying degrees of trypanocidal activity *in vitro*. The roots of *T. superba* and *K. senegalensis*, the stem of T. superba and the leaf of A. africana were the most effective with a MLC of 3 mg/ml; compared to 5.4 mg/ml for diminazene aceturate, the reference drug. *A. africana* stem bark also had an MLC of 5.4 mg/ml in the study. The extracts were also analyzed for hemolytic activity, using washed bovine red blood cells in order to ascertain if any relationship between their hemolytic and antitrypanosomal activities. In the *in vivo* analysis, only the *T. superba* root bark extract totally inhibited the growth of parasites in both rats and mice; all the other root bark extracts resulted in parasite clearance in rats only. The duration of clearance in all cases was 48 h, with relapse parasitaemia occurring on the 3rd day post-administration of the extracts. Another study by Abu and co-workers [19] evaluated the *In vitro* antitrypanosomal activity of crude extracts of eight medicinal plants from Nigeria, the plants consist of *Anthocleista vogelii, Blighia unijugata, Cussonia arborea, Gardenia erubescens, Hymenocardia acida, Lophira lanceolata, Stereospermum kunthianum and Uapaca togoensis.* The results showed that *Hymenocardia acida* extracts were active against *T. B. brucei* at minimum inhibitory concentration of 2.5 mg/ml. This is the first report of antitrypanosomal activity of *Gardenia erubescens* and *Lophira lanceolata* which were effective at minimum inhibitory concentration of 20 mg/ml. Phytochemical screening of H. acida extracts showed the presence of saponins, tannins, alkaloids and flavonoids.

Olukunle and co-workers [20] investigated the antitrypanosomal activities of aqueous extracts of 5 medicinal plants including the root bark of *Morinda morindiodes* and leaves of *Tithonia diversifolia*, *Lippia multiflora*, *Ocimum gratissimum* and *Acalypha wilkesiana* in albino rats infected with *T. b. brucei*. The plant extracts at 400mg/kg body weight (of rats) were administered once daily for 7 days in an established infection of 5 x 106 parasitaemia before starting treatment. There was significant reduction in parasitaemia ($P< 0.05$) on the 3rd day of treatment in rats treated with *M. morindiodes*, *T. diversifolia* and *A. wilkesiana* but parasitaemia later increased till survival time. *Morinda morindiodes*, a plant well known for its potents antimalarial effect, has it root bark extracts exhibiting the highest value of mean survival time (12.6+0.7) days this study. The study of [21] evaluated different extracts of *M. oleifera* parts for their anti-trypanosomal activity and broad phytochemical classes. The secondary metabolites reported includes alkaloids, resins and saponins. *In vitro*, the petroleum ether extract of the root bark, chloroform extract of the stem bark, methanol extracts of the stem and the aqueous extracts of all parts were active at 4 and 2 mg/ ml doses. The chloroform and methanol extracts of the leaves, and the chloroform extract of the root also possessed strong activity. *In vivo*, methanol and aqueous extracts of the leaves, stem and root barks at 300mg/kg displayed significant effect on parasitaemia and survival period, indicating their antitrypanosomal potential.

In vitro and *in vivo* antitrypanosomal effects as well as reagent-based chemical screening of the aqueous and methanolic extracts of the roots, leaves and stem bark of *T. avicennioides* were undertaken [22]. These results suggest that the use of *T. avicennioides* for management of trypanosomiasis in traditional medicine has scientific basis, and thus warrants further detailed evaluation. Mann [23] investigated the *In vivo* antitrypanosomal activity of four medicinal plants including *Acacia nilotica*, *Bombax buonopozense*, *T. avicennioides* and *Zanthoxylum zanthoxyloides* traditionally used for treatment of sleeping sickness in Nupeland. Methanol extracts of different parts of each plant (stem barks and fruits) were obtained and evaluated for their *In vivo* antitrypanosomal activities against *Trypanosoma brucei brucei*. Methanol extracts of *A. nilotica* (stem bark), *B. buonopozense* (stem bark), *T. avicennioides* (round fruit) and *Z. zanthoxyloides* (stem bark) were effective on trypanosomes. The extracts of *A. nilotica* and *B. buonopozense* exhibited antitrypanosomal effects at 200 and 300 mg/kg body weight respectively. While the extracts of *T. avicennioides* and *Z. zanthoxyloides* showed trypanostatic effects and could not clear the parasites completely. The methanol extracts of these plants contain metabolites that are associated with antitrypanosomal effects; therefore, these medicinal plants may be sources of new compounds that may be active against *T. b. brucei*.

Ogbadoyi and co-workers [24] investigated the methanolic extract of stem bark of the *Acacia nilotica* for its therapeutic effects in experimental African trypanosomiasis. Acute toxicity studies were also conducted. Crude extract of 70% v/v (Methanol/Water) at a dose of 400mg kg-1 body weight per day completely cured the experimental *T. b. brucei* infection in mice, while doses of 50, 100, 200, 300, and 400mgkg-1 body weight per day of the partially purified extract completely cured the experimental infection in mice within two days. Sub inoculation of blood and cerebrospinal fluid drawn from the cured mice into healthy mice failed to produce any infection within 28 days of post inoculation. Phytochemical analysis showed the presence of carbohydrates, saponin, tannin and cardiac glycoside. LD50 of the partially purified extract was found to be 2000mg/kg body weight, the extract being acutely toxic at a dose of 1600mgkg-1 body weight. The antitrypanosomal efficacy of different doses of *Cucumis metuliferus* pulp extract was investigated in rabbits [25]. The work reported that, *C. metuliferus* has antitrypanosomal properties at 500 to 1000 mg/kg body weight. It promotes weight gain, reduces anaemia and controls hepatomegaly and splenomegaly in *T. b. brucei* infection. The extract is potentially useful in the management of *anaemia*, which is a major pathological feature of African trypanosomiasis and other pathological features such as hepatomegaly and splenomegaly.

In vitro antitrypanosomal activity of 36 plant extracts from 10 plant species from Nigerian ethnomedicine was evaluated against bloodstream forms of *T. b. rhodesiense* STIB 900 [26]. The study revealed that ethyl acetate extract of leaves of *Ocimum gratissimum* Linn. (Labiatae) showed the highest antitrypanosomal activity (IC50 of 2.08±0.01 μg/ml) and a high selective index of 29. Also, the hexane, ethyl acetate, or methanol extracts of *Trema orientalis*, *Pericopsis laxiflora*, *Jatropha curcas*, *Terminalia catappa*, and *Vitex doniana* displayed remarkable antitrypanosomal activity (IC50 2.1–17.2 μg/ml) with high selectivity indices (20–80) for trypanosomes. The antitrypanosomal activity of T. *catappa* and *T. orientalis* against T. *brucei rhodesiense* (STIB 900) is being reported for the first time in Nigerian ethnomedicine, and these plants could be a potential source of antitrypanosomal agents.

In vitro and *in vivo* Antitrypanosomal activity of saponins-rich fraction of *Calotropis procera* leaves as well as the effect of the fraction on the parasite-induced anemia was investigated [27]. The extract did not demonstrate an *in vitro* antitrypanosomal activity. However, the *C. Procera* extract treatments did not significantly ($P>0.05$) keep the parasites lower than the infected untreated groups. At the end of the experiment, all *T. evansi* infected rats developed anemia whose severity was not significantly ($P>0.05$) ameliorated by the cpsf treatment. They concluded that, saponins derived from *C. procera* leaves could not elicit *in vitro* and *in vivo* activities against *T. evans.*

The study of [28] investigated nine selected Nigerian medicinal plants for antitrypanosomal activity with a view to providing information on the potential role of any of the nine plants as an antitrypanosomal and/or anti-inflammatory agents. Extracts of *Khaya senegalensis, Harungana madagascariensis, Terminalia ivorensis, Curcuma longa, Ocimum gratissimum* and *Alcornea cordifolia* showed weak anti-trypanosomal effect and did not exhibit significant clearance in parasitemia at the test dose administered compared with the positive control. However, the leaf extract of *U. chamae* and its hexane fraction demonstrated a significant response ($P < 0.01$). The fraction at 1000 mg/kg inhibited oedema by 107%. *Uvaria chamae* demonstrated both antitrypanosomal and anti-inflammatory properties by increasing the survival time of infected mice due to reduction in parasitemia caused by *T. brucei brucei.*

Feyera and co-workers [10] screened the hydromethanolic and dichloromethane (DCM) crude extracts of aerial parts of *Artemisia abyssinica* for *in vivo* antitrypanosomal activity against *T. congolense* isolate in mice. The study established that aerial parts of *A. abyssinica* have antitrypanosomal potential and can be considered a potential source of new drugs for the treatment of tropical diseases caused by trypanosomes. Ismaila and co-workers [29] carried out *In vitro* antitrypanosomal activity test on aqueous extracts of dried leaves of *Acacia albida, Artemisia absinthium, Bryophyllum pinnatum, Gongronema latifolium, Holarrhena floribunda, Leptadenia hastata, Pericopsis laxiflora* and dried stem barks of *A. albida* and *P. laxiflora*. The study discovered that the stem bark extracts of *A. albida* and *P. laxiflora* were most active against both *Trypanosoma evansi* and *Trypanosoma congolense*. The study also provides scientific evidence for the use of *A. albida*, and *P. laxiflora* for the treatment of trypanosomosis and diseases associated with oxidative stress.

The ethanolic leaf extract of *Carissa Spinarum* was evaluated for *in vivo* anti-trypanosomal activity against federa strain of *T. b. brucei* in albino mice [30]. Four days suppressive, curative effect against established infection and prophylactic models of anti-trypanosomal studies were carried out. The median lethal dose of the extract was determined to be ≥ 100mg ⁄ kg body weight. The extract (12.5, 25, 50mg / kg) exerted some dose dependent suppressive effects at the different levels of infections tested, with no significant curative effects recorded. *In vitro* antitrypanosomal and antioxidant activity of extracts and compounds obtained from *Moringa oleifera* leaves were evaluated [31]. The work reported that, crude ethyl acetate extract was subjected to different chromatographic techniques to obtain a fraction showing antitrypanosomal activity (MIC 25µg/ml). In addition, antioxidant activities of the crude extracts were established on the free radical scavenging activity of DPPH. The extracts showed strong antioxidant activity with 50% efficient concentration (EC50) values of 24 and 44 µg/ml for the ethyl acetate and methanol extracts respectively. The results of this study suggest the potentials of ethyl acetate extract of *M. oleifera* in treating trypanosomiasis a disease caused by *T. brucei*.

Reference [32] studied the *In vitro* and *In vivo* antitrypanosomal activity of the ethanolic leaf extract of *Tithonia diversifolia* in albino rats. Phytochemical study and acute toxicity test were carried out for the plant extract using standard procedure. The phytochemical results reveal the presence of terpenoids, steroids, reducing sugar, alkaloids, phenol and flavonoids in high concentration. The lethality dose (LD50) result of the plants extract was found to be equal or greater than 5000mg/kg body weight. The ethanol extracts showed appreciably high *in-vitro* and *in-vivo* anti-trypanosomal activities compared to the reference drug. Motility of *T. brucei* was stopped by the ethanol extract of the leaf after 40 minutes at concentration of 4mg/kg body weight. The packed cell volume (PCV) showed non-significant ($P>0.05$) increase in the rats infected with *T. brucei brucei* treated with varying doses of *T. diversifolia* compared with the PCV of rats infected and administered 0.5ml of distilled water. The *in-vitro* and *in-vivo* anti-trypanosomial activity exhibited by the extract might be attributed to the bioactive compounds present in the plant extract.

In vitro cytotoxicity test of methanolic plant extract (MPE) of *E. officinalis* at different concentrations (1.56-100 µg ml-1) was performed on Vero cells grown in Dulbecco's Modified Eagle Medium (DMEM) without fetal calf serum at appropriate conditions [33]. Significant trypanocidal activity was observed at 250 µg ml-1 of MPE (100%) of *E. officinalis* and trypanosomes were not detected after 5 h of incubation, which was statistically equivalent to diminazine aceturate (50µg/ml) standard drug at 4 h. For 250 µg ml-1 of MPE of E. officinalis (50%), there was drastic reduction at the end of 5 h incubation but not complete killing of trypanosomes. Furthermore, at 500 µg ml-1, trypanosomes were not detectable at 4 h of incubation. Extract of *E. officinalis* and diminazine aceturate were cytotoxic to Vero cells in all concentrations except at 1.56-6. 25 µg ml-1. Almost similar finding were reported by [34] using different plant. The work evaluated the MPE of *C. sinensis* leaves at different concentrations (250-1000 µg/ml) against *Trypansoma evansi* on Vero cell line grown in DMEM at appropriate conditions. The *In vitro* anti-trypanosomal activity of *C. sinensis* leaves varied from immobilization, reduction and killing of trypanosomes at different concentrations used. At a concentration of 250 µg ml-1, there was drastic reduction and complete killing of trypanosomes occurred at the same concentration (40.00±0.0 to 0.0±0.0) in 4 h of incubation, which is comparable to 4 h of diminazine aceturate.

Balogun and others [11] reported that, *Terminalia macroptera* had shown *in vivo* antitrypanosomal activity against *T. b. brucei* as evidences from the results revealed it`s efficacy on the parasitaemia level, increased life span of the treated rats beyond that of the untreated rats. Thus, the anti-trypanosomal activity of *T. macroptera* may be attributed to its high antioxidant activity and its terpenoids, phenol, flavonoids and alkaloid contents as revealed by gas chromatography mass spectrometer. The work of Atawodi (2005) cited in [35], tested about forty tropical plants harvested from the savannah against *T. b. brucei*. Of the plants studied, only 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. The results suggested that tropical plants could be a very promising source of new generations for trypanocidal activity. The study conducted by [36], evaluated the crude and fractionated ethanolic extracts of *Chrysophyllum albidum* (African Star Apple) leaves for anti-trypanosomal potentials. This was done by crude ethanolic extraction and fractionation of the extract using column chromatography where four fractions were obtained.

Oguntoye *et al.,* [37] reported that, chloroform fractions of the leaves extract of *Datura metel* and *C. procera*, hexane fractions of the whole plant of *Hymenocardia acida* with the leaves of *Morinda lucida* and the methanol fractions of the leaves and stem of *Nymphea odorata* showed significant activity against *T. b. brucei* blood stage trypamastigotes with IC50 (µg/ml) values generally less than 5 µg/mL.

IV. FUTURE EXPECTATIONS

It is of paramount importance for Nigerian scientists especially Chemists, Biologist among others to embark and devise new automated bioassays with special emphasis on high through-put procedures that can screen and process data from a panoply of phytochemicals within shorter time lapse [38]. These procedures should also attempt to rule out false positive hits and dereplication methods to remove nuisance compounds. Furthermore, despite continuous comprehensive and mechanism-orientated evaluation of medicinal plants in Nigeria, there is still limited information regarding procedures to be adopted for quality assurance, authentication and standardization of crude plant products [38]. Finally, randomized controlled trials using standardized products or products containing pure plant extracts must be carried out and reported for each claim.

V. CONCLUSION

Nigeria is naturally blessed with both savannah and tropical rainforests vegetation and these offer a wide distribution of plants believed to possesses secondary metabolites which are responsible for treating or curing various diseases. The use of medicinal plants is very advantageous in terms of resource on chemical and biological research in natural products area. The present review reported the *in vivo* and *in vitro* antitrypanosomal activity of Nigerian medicinal plants. Almost seventy Nigerian medicinal plants were reported for antitrypanosomal activity in this paper. The paper recommended that further research on other medicinal plants should be investigated for antitrypanosomal activities.

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