Academy Journal of Multidisciplinary Doctoral Research [AJMDR]
Volume 1, Issue 1, 2023 ISSN: 2992-4669|| eISSN: 1116-3321

The Studies of Anti-Trypanosomal Activity of Selected Plants Extracts against Dimenazene Aceturate® Resistant Strains of *Trypanosoma Brucei* and *T. Congolense* Isolates.

Yusuf Rabe

Department of Biological Sciences, Nigerian Defence Academy, Kaduna State

Corresponding Author's Email: yusuf.rabe2020@nda.edu.ng

Received: 25-05-23
Accepted: 20-06-23
Published: 17-08-23

Abstract

African trypanosomiasis is a parasitic disease caused by arthropod vectors disease is causing serious threats to the lives of millions people as well as animals, especially cattle worldwide. Plants in Nigeria are known to contain medicinal properties within a large variety of their chemical structures, and many have been screened and tested against anti-trypanosomal activity, with the effort of finding new drugs against the disease on plants and their products with anti-trypanosomal activity from Nigerian flora were surveyed based on the available publication as at the time of compilation of this report. About 40 plants were identified, with 30 compounds as potential active agents and presented in the text. This review indicates the suitability of Nigerian flora in providing a greater advantage in the search for new and efficient trypanocidal molecules that could provide a better result against dimenazene aceturate resistance strains of the parasites to most of the conventional drugs.

Keywords: Nigeria; Trypanosomiasis; Medicinal Plants; Dimenazene Aceturate.

1.0 INTRODUCTION

African trypanosomiasis is a protozoan parasitic disease of the genus *Trypanosoma*. *Trypanosoma congolense* (*T. congolense*), *Trypanosoma vivax*, and *Trypanosoma brucei brucei* (*T. b. brucei*) are the species causing African animal trypanosomosis (AAT) which is referred to as nagana in West Africa and *T. rhodesiense* and *T. b. gambiense* are responsible for sleeping sickness called Human African trypanosomiasis, while *T. evansi* and *T. equiperdum* causes Surra disease and dourine respectively. The disease is transmitted by a bite of the arthropod vector-tsetse fly (*Glossina* species) (D' Archivio *et al.*, 2011). Trypanosomiasis is an important livestock disease. Causing major clinical significance in ruminant animals and extending even to other tsetse-free zones. (Joshua *et al.*, 1983; Ayodele *et al.*, 2013). There have been reported cases of disease outbreaks in many communities in Nigeria, although there is an endemic settlement of the old Gboko. (Airauhi *et al.*, 2001; Edeghere *et al.*, 1998). There are various prevalence rates of the diseases among the different breeds of animals in Nigeria, previous studies reported between 4.8% to 6.9%. (Idehen *et al.*, 2018).

1.1 Forms of Human African Trypanosomiasis

Human African trypanosomiasis occurs in two forms, depending on the species of the parasites (and their subs-species):

i. *Trypanosoma brucei gambiense*: This specie is found in 24 countries in West Africa as well as Central Africa. An individual can be infected with the disease without noticing, until after some weeks or months. Hence this disease account for almost 97% of sleeping sickness reported cases. The chronic stage result in the central nervous system being affected (World Health Organization, fact sheets, 2020).
ii. *Trypanosoma brucei rhodesiense* is currently found in 13 countries in both eastern and southern Africa. Currently, this form represents less than 3% of reported cases and can advance to an acute infection. Signs and symptoms manifest weeks or months after infection. It develops faster and affects the central nervous system. The disease is only reported in Uganda (WHO, fact sheets, 2020).

1.2 Animal Trypanosomiasis

Parasite species of the genus Trypanosoma are pathogenic to animals and cause disease to animals. Nagana which affects domestic animals such as cattle, sheep, and pigs and causes greater economic loss. While Surra mainly affects wild animals such as buffalo, antelope, etc. Human pathogen especially *T. b. rhodesiense* parasites is also harbored by domestic and wild animals serving as the reservoir. And they can as well act as a reservforr to *T. b. gambiense. However, their specific role as a reservoir is not known.* (WHO, fact sheets 2020).

1.3 Major Human Epidemics

There have been several epidemics in Africa over the last century:

i. Between 1896 and 1906, mostly in Uganda and the Congo Basin;
ii. In 1920 in several African countries; and
iii. The most recent epidemic started in 1970 and lasted until the late 1990s. (WHO, fact sheets, 2020).

The 1920 epidemic put a greater percentage of people at risk. Toward the middle of the 1960s, the cases were less than 5000 due to the control put in place. And the disease resurfaces in 1970 reaching epidemic proportions in many parts of the world. The efforts of various organizations (NGOs) including the WHO in the 1990s and early 2000 reduced the spread of the disease (WHO, fact sheets, 2020).

However, the cases of HAT dropped between 2000 and 2012 due to the measures put in place by the WHO as part of the target to eliminate neglected tropical diseases by 2020 and interrupt their transmission by 2030. (WHO, fact sheets, 2020).

1.3 Disease Burden

Sleeping sickness has put millions of people at risk in more than 36 countries in sub-Saharan Africa. Many of the affected individuals live in a remote area with poor access to good and quality drinking water, and health facilities which hinder proper diagnosis and facilitate the transmission of the disease (ref).

i. In 1998, almost 40 000 cases were reported, but estimates were that 300 000 cases were undiagnosed and therefore untreated.
ii. During the last epidemic the prevalence reached 50% in several villages in Angola, the Democratic Republic of the Congo, and South Sudan. Sleeping sickness was the first or second greatest cause of mortality in those communities, even ahead of HIV/AIDS (WHO, fact sheet, 2020).
iii. In 2009, after continued control efforts, the number of cases reported dropped below 10 000 (9 878) for the first time in 50 years. This decline in a number of cases has continued with 992 and 663 new cases reported in 2019 and 2020

respectively, the lowest level since the start of systematic global data collection 80 years ago. The estimated population at risk is 55 million people for the period 2016–2020; with only 3 million people at moderate or higher risk (WHO fact sheets 2020) (WHO, fact sheet, 2020).

1.4 Current Disease Distribution

The incidence of the disease differs from one country to another and between different regions of the country.

i. 70% of reported cases occurred in the Democratic Republic of the Congo, in the last five years, and an average of fewer than 1,000 cases were declared annually (WHO, fact sheet, 2020).
ii. Central African Republic, Congo, Gabon, Chad, Angola, Guinea, Malawi, and South Sudan recorded between 10 and 100 new cases in 2019, while Cameroon, Côte d'Ivoire, Equatorial Guinea, Uganda, United Republic of Zambia, Tanzania, and Zimbabwe reported between 1 and 10 new cases.
iii. Countries such as Burkina Faso, Ghana, Kenya, and Nigeria, have reported sporadic cases in the last 10 years (WHO, fact sheet, 2020).
iv. Benin, Gambia, Guinea Bissau, Liberia, Botswana, Burundi, Ethiopia Mali, Mozambique, Namibia, Niger, Rwanda, Senegal, Sierra Leone, Swaziland, and Togo have not reported any new cases for over 10 years period. Transmission of the disease seems to have stopped in some of these countries but there are still some areas where it is difficult to assess the exact situation because of the heterogeneity and social circumstances/difficult accessibility that hinder surveillance and other diagnostic activities (WHO, fact sheets, 2020).

1.5 Infection and Symptoms

The disease is mostly transmitted through the bite of an infected tsetse fly but there are other ways in which people are infected:

i. Mother-to-child infection: the trypanosome can cross the placenta and infect the fetus (World Health Organization, fact sheets, 2020).
ii. Mechanical transmission through other blood-sucking insects is possible, however, it is difficult to assess its epidemiological impact (World Health Organization, fact sheets, 2020).
iii. Accidental infections have occurred in laboratories due to pricks with contaminated needles (World Health Organization, fact sheet, 2020).
iv. Transmission of the parasite through sexual contact has been reported (World Health Organization, fact sheets, 2020).

In the initial stage, the trypanosomes multiply in subcutaneous tissues, blood, and lymph. This is also called the haemo-lymphatic stage, which is accompanied by fever, headaches, enlarged lymph nodes, joint pains, and itching (WHO, fact sheets, 2020).

In the subsequent stage, the parasites cross the blood-brain barrier and infect the central nervous system. This is called the neurological or meaning-encephalic stage. The more obvious sign and symptoms appear here: behavioral change, confusion, sensory disturbances, and poor coordination. the sleep cycle interfered with, which is the important feature that gives the disease its name. Failure to treat it, may result in a serious fatality. (WHO fact sheets 2020).

The economic loss due to trypanosomiasis in Africa is estimated to be valued at 5 billion US dollars. And it was also estimated by the WHO, that about 60 million people were at risk and new cases annually reached up to 300, 000. Fewer cases are being diagnosed and treated. Thus, the cases reported due to the measures put in place by the WHO in 2004. Now that the cases in Africa fall between 50,000 to 70,000 annually. The

number of new cases reported fell below 10,000 as of 2009, this happened for the first time in 50 years and the estimated number of actual cases is currently 30,000. This curve continued in 2012, with 7216 cases reported (Abenga *et al.,* 2005).

Suramin, pentamidine, melarsoprol, eflornithine, arsobal and mel B are the six (6) drugs of choice against the disease, five of which were developed more than 3 decades ago. While homidium, isometamidium and diminazene aceturate are used in animal infections each of these drugs has one or more of these challenges: from being expensive to highly toxic, or need parenteral administration and some faced parasites resistance with time. However, effort put in place by the NGOs, including WHO, with the aim of eliminating HAT is yielding a fruitful results and success is being recorded. The neglected tropical disease initiative (DND*i*) developed fexinidazole (drug for neglected tropical disease initiative) as a new oral drug with a huge success being recorded, and it has entered the last phase of its clinical trial in patience with fatal case of sleeping sickness. With the hope that fexinidazole would solve the problems/challenges and limitations of current chemotherapeutic options from other drugs (Masser *et al.,* 2013, Amachi *et al.,* 2000 and Kaisar *et al.,* 2011). Thus, several reviews on medicinal plants used in treatment of trypanosomiasis have been published.

1.6 Statement of the Problem

African Trypanosomiasis is one of the neglected tropical diseases, causing serious threats to both humans and wild/domesticated animals. Activity of plants with potential anti-trypanosomal properties has not been widely reported, as compared to other neglected tropical diseases, most especially protozoans such as malaria. Drugs and other chemotherapy currently being used as a source of controlling the disease is still facing parasites continues resistance, while some of the drugs are toxic, others need parenteral administration, or expensive and are not affordable by the farmers or the majority of the populace. The antigenic variation of the parasites has discouraged many pharmaceutical industries to develop new drugs/ vaccine that could counter the parasites resistance against the conventional drugs being used. The approved drugs for trypanosomiasis have to be administered through intravenous route thus requiring medical and veterinary facilities and specialized staff which often are not readily available in rural sub-Saharan Africa. Side effects associated with the use of the current anti-trypanocidal drugs are fatal, in some life-threatening. Diminazene aceturate (i.e drug melarsoprol) for instance, causes a serious reactive encephalopathy in 5-10 % of the cases, more than half are fatal. Other common side effects include, abdominal colic, vomiting, and peripheral neuropathy. There are also reports of increasing treatment failures. Hence urgent need for new drugs from our local plants product against African trypanosomiasis which are safe, effective and can be applied externally or orally administered.

1.7 Justification

Low foetal weights, premature births and neonatal losses, poor reproductive performance and poor lactation are the huge reproductive losses in livestock due to AAT (Faye *et al*., 2004). Testicular degeneration, reduced libido, orchitis, and poor semen characteristics have been established in infected animals. (Kabir, 2014). Adamu *et al*. (2007) also degeneration of testis, and low libido, making infected animal unfit for breeding. Despite the effort to eradicate the disease it has proved difficult to eradicate. Thus, the search for medicinal plants with trypanocidal activities continue to generate a lot of research interest by the parasitologist (Hoet *et al*., 2004; Samson, 2005). Although recent reports indicate antitrypanosomal activity exists in some medicinal plants (Wurochekke *et al*., 2004; Ibrahim *et al*., 2008; Shuaibu *et al*., 2008), the potentials of many other plants used in folkloric medicine in Nigeria are yet to be investigated. This study is designed to investigate the in vitro antitrypanosomal activity of some selected plants in Nigeria.

1.8 Aim

The aim of the study is to evaluate the anti-trypanosomal activity of extracts of *Cymbopogon citratus Azadirachta indica, Moringa Oliefera, Garcia kola* and *Psidium guajava,* against

dimenazene aceturate resistant strains of *T. congolense and T. b. brucei* isolates.

1.8 Objectives

i. To carryout *in vitro* screening of the extracts of root barks, leaves and stem barks of *Cymbopogon citratus*, *Azadirachta indica, Moringa Oliefera, Garcia kola,* and *Psidium guajava,* against dimenazene aceturate resistant strains of *T. congolense and T. b. brucei* isolates.

ii. To evaluate toxicity of the antitrypanosomal extracts of root barks, leaves and stem barks of *Cymbopogon citratus, Azadirachta indica, Moringa Oliefera, Garcia kola,* and *Psidium guajava,* against dimenazene aceturate resistant strains of *T. congolense and T. b. brucei* isolates *in vivo.*

iii. To determine the efficacy of the active extracts of root barks, leaves and stem barks of *Cymbopogon citratus, Azadirachta indica, Moringa Oliefera, Garcia kola,* and *Psidium guajava,* against dimenazene aceturate resistant strains of *T. congolense and T. b. brucei* isolates *in vivo*

iv. To carryout *in vitro* isolation and purification of anti-trypanosomal properties of the active extracts.

2.0 MATERIALS AND METHODS

Inclusion Criteria: Plants parts targeted for these experiments were selected and literatures related to the research study area were included in this article.

Exclusion Criteria: Other plants and their products were rejected, and only *Trypanosoma congolense* infected animal/strain of the parasite were used/inoculated, to test the efficacies of the selected plants and reasons for resistance against dimenaze aceturate drugs.

The methods employed in gathering data for the study is both qualitative and quantitative.

Plant materials: *Cymbopogon citratus, Azadirachta indica, Moringa Oliefera, Garcia kola, Psidium guajava* selected for their ethnopharmacological properties. Parts of the plants (leaf, stem root) were collected at different time in the literatures adopted, within the environs of Kaduna, capital of Kaduna state, Nigeria and were identified in the Herbarium of the Department of Biological Sciences, Nigerian Defence Academy, Kaduna Voucher specimens (Voucher Number YR 1928, YR 1929, YR 1930 and YR 1931) were deposited at the University herbarium Prior to identification.

Preparation of crude extracts: Plant parts (leaf, stem and root) were washed and allow to dry freely at room temperature (28^0C – 30^0C) for a period of one week, then pulverized and stored in air-tight containers until needed. The material in powdered (100g) was mixed in 500ml of methanol/distilled water and stirred intermittently for the period of 48 hours at room temperature (28^0C – 30^0C). The material was then filtered using sterile cotton wool and (No.1) Whitman filter paper; the residue was resuspended in the same amount of solvent and then filtered again three more times. The aqueous filtrates obtained previously were concentrated to dryness over water bath at 50^0C whereas the ethanolic filtrates were dried under the electric fan. The extracts were stored in airtight containers at 4^0C until needed.

Parasite: *T. congolense and T. b. brucei* stabilates were obtained from the National Institute for Trypanosomiasis Research Kaduna, Nigeria. The parasites were maintained in the laboratory after inoculating in mice. Blood collected from a donor animal at peak parasitaemia (10^7 parasites/ml of blood) were used for in vitro antitrypanosomal assay experiment.

3.0 RESULTS AND DISCUSSION

The results of some of the literature searched online, from google scholar, science directs, research gate among others were compiled in a table below:

Table 1: Some Of The Plants/Parts And Their Uses

Family	Species	Traditional use	Plants Parts
	Acacia nilotica	Treatment of cancer tumours of ear/eye	Stem Bark
	Afzelia Africana	Trypanosomiasis, convulsion, hernia	Pulp
	Parkia clappertoniana	dental caries, conjunctivitis	Root
	Piliostigma reticulatum	Ulcer, boils, wounds, cancer, syphilis and diarrhoea	Leaves
	Prosopis Africana	Used to prepare food in Northern Nigeria	Stem Bark
	Afrormosia laxiflora	Epilepsy and psychosis	Leaves
	Erythrophleum suaveolus	Arthritis, rheumatism, dropsy, swelling, eye treatment	Stem Bark
	Lonchocarpus laxiflorus	Dermatitis, headache, intestinal worm, jaundice, ulcer	Stem Bark
	Swartzia madagascariensis	Poison arrow and fishing, insecticide	Root
	Senna occidentalis	Bacterial and malaria infections	Leaves
Fagaceae	*Quercus borealis*	Dyspnea, nausea, emesis, diarrhea	Leaves
Hymenocardiaceae	*Hymenocardia acida*	Hypertension, Root, Stem Leaves	
	Hyptis spicigera	Cold, insecticides	Leaves
Lauraceae	*Cassytha filiformis*	Food and infectious diseases	Leaves
Loganiaceae	*Anthocleista vogelii*	Purgative, diuretic, ulcer, stomach-ache Leaves	
Meliaceae	*Syzygium guineense*	Used to bath ill person	Stem Bark
	Eucalyptus camaldulensis	For the treatment of malaria and typhoid fevers	
Ochnaceae	*Lophira lanceolata*	Dermatosis, toothache, muscular tiredness	Leaves
	Ximenia americana	Treatment of fever, jaundice, impotence, sleeping sickness	Stem Bark
Plantaginaceae	*Picrorhiza kurroa*	Treatment of asthma, bronchitis, dysentery and malaria	Pulp
Poaceae	*Canarium schweinfurthii*	Burnt for fumigation	Stem Bark
Rubiaceae	*Gardenia erubescens*	Used as dye	Leaves
	Keetia leucantha	To treat malaria	Leaves
	Morinda lucida	Used to treat malaria	Leaves
Rutaceae	*Zanthoxylum zanthoxyloides*	Stomach disorder, worm infection	Stem Bark
Verbenaceace	*Vitex doniana*	Anemia, gonorrhea, dysentery, fertility	Leaves
	Vitex simplicifolia	To treat malaria	Leaves
Vitaceae	*Cissus multistriata*	For the management of protein deficiency	Leaves
Zingiberaceae	*Zingiber officinale*	Used to treat gastrointestinal diseases, nausea, emesis, dyspnea, diarrhea and muscular pain	Leaves

Source: Ngozi *et al.*, 2015

Table 2: Plants Parts Tested Against the Parasites

Trypanosomes	**Medicinal Plants**	**Parts Tested**	**References**
T. b. brucei	*Khaya senegalensis*	Flower, Stem Bark	Atawodi *et al*., 2003
	Terminalia avicennoides	Flower	Atawodi *et al*., 2003
	Prosopis africana	Flower	Atawodi *et al*., 2003
	Sterculia setigera	Flower	Atawodi *et al*., 2003
	Piliostigma reticulatum	Flower	Atawodi *et al*., 2003
	Anogeissus leiocarpus	Stem bark	Atawodi *et al*., 2003
	Sclerocary birrea	Stem bark	Atawodi *et al*., 2003
	Commiphora kerstngii	Stem bark	Mbaya *et al.*, 2010
	Azadirachta indica	Root bark	Aderbauer *et al.*, 2008
	Securidaca longependuncullata	Stem bark	Wurochekke *et al*.,2004
	Lawsonia inermis	Stem bark	Ogbunugafor *et al.*, 2008
	Mitragyna ciliata	Leaves, twigs	Sara *et al.*, 2004
	Cassia sieberiana	Stem bark	Particia *et al.*, 2005
	Bachris trimera	Stem bark	Sara *et al.*, 2004
	*Prunus domestic*a	Stem bark	Kamanzi *et al.*, 2004
	Sambucus canadensis	Stem bark	Kamanzi *et al.*, 2004
	Tanacetum parthenium	Stem bark	Atawodi *et al.*, 2003
	Matricaria chamomilla	Stem bark, Leaves	Shuaiba *et al.*, 2008
	Piper regnellii	Leaves	Atawodi *et al.*, 2003
	Stryphnodendron adstringens	Leaves, Stem bark and Roots	Particia *et al.*, 2005 Particia *et al.*, 2005
	Pericocopsis laxiflora	Leaves, Stem bark	Particia *et al.*, 2005
	Trichilia emetica	Stem bark	Particia *et al.*, 2005
	Strychnos spinosa	Stem bark	Particia *et al.*, 2005
	Albizia zygia	Stem bark	Particia *et al.*, 2005
	Enantia polycarpa	Stem bark	Particia *et al.*, 2005

examining cerebrospinal fluid (WHO, fact sheets, 2020).

3.1 Disease Management:

Diagnosis

Disease management is made in 3 steps:

i. Screening for potential infection. Using body fluids (serological tests) which readily available for *T. b.gambiense* only) and checking swollen cervical lymph nodes for any clinical signs (WHO, fact sheets, 2020).
ii. General serological diagnosis.
iii. Checking the disease progression. This includes medical examination, as well as those living within tsetsefly zone is recommended. And this require capital as well as human and material resources, which are not readily available in Africa where the disease is predominant. As a

Early diagnosis is recommended to avoid having complication in the neurological stages and to fast-track treatment (WHO, fact sheets, 2020).

The asymptomatic period in sleeping sickness which is taking longer period before the proliferation of sign and symptoms is the most challenging period, that is why many people are at risk of getting infected with trypanosome (*T.b gambiense*) and later sleeping sickness, that's the reason why screening of the population especially

result, some individuals already infected may die before they are diagnosed. (WHO, fact sheets, 2020).

Treatment

The type of treatment depends on the type and stage of the disease, the earlier treatment the better, and must be accompanied by a follow of one year, to a certain the curability of the disease. Serological diagnosis is often recommended for the treatment after sample is taking from cerebrospinal fluid, to avoid the parasite's ability to thrive after some period of time. The type of treatment depends on the form of the disease and the disease stage. (WHO, fact sheets, 2020).

To a certain the treatment success in the later stage depends on drugs ability to cross the blood-brain barrier to reach the parasite point (WHO, fact sheets, 2020).

Treatment guidelines for human African trypanosomiasis (*gambiense)* were issued in 2019 by WHO. Six different drugs with different compounds each to give a desired effect are used for the treatment of sleeping sickness. These drugs are donated to private partners in collaboration with WHO by the manufacturing companies to be issued free of charge to trypanosomiasis endemic countries (WHO, fact sheets, 2020).

The first two (2) Drugs used in the treatment of initial stage:

i. **Pentamidine:** this was discovered in 1940, and is used for the treatment of the initial stage of sleeping sickness caused by *T. b. gambiense*. Thou it has a minimal side effects. (WHO, fact sheets, 2020).
ii. **Suramin:** this was discovered in 1920, it is used also for the treatment of the initial stage of *T. b. rhodesiense*. It causes some undesirable effects, like nephrotoxicity and in some cases allergic reactions (WHO, fact sheets, 2020).

The second four (4) Drugs used in the treatment of later stage:

i. **Melarsoprol:** this was discovered in 1949, used for the treatment of *rhodesiense* and *gambiense* infections. It is derived from arsenic and has many undesirable side effects, the most lethal is the reactive encephalopathy (encephalopathic syndrome) which is often be fatal (3% to 10%). Hence, it is recommended as first-line treatment for the *rhodesiense*, but not commonly used in the treatment of *gambiense* (WHO, fact sheets, 2020).
ii. **Eflornithine:** This is only effective against T.b gambiense, quick and better action than melarsoprol, registered in 1990. Used as monotheraphy and in combination with nifurtimox (as part of the Nifurtimox-eflornithine combination therapy, NECT). Thou regimen is highly complex and cumbersome to apply by the patience (WHO, fact sheets, 2020).
iii. **Nifurtimox:** Is a combination therapy that combine the Nifurtimox-eflornithine, NECT, introduced in 2009. This drug simplifies the use of eflornithine by reducing the duration of treatment and the number of IV perfusions, it has not been studied for *T.b. rhodesiense*. Nifurtimox is registered for the treatment of Chagas disease also known as American trypanosomiasis but not for HAT. The drugs are distributed free of charge by the WHO to endemic countries with manual/user guide instructions attached. (WHO, fact sheets, 2020).

Drugs used in the treatment of both stages:

Fexinidazole is used an orally for the treatment of *gambiense* (HAT) It was incorporated in 2019 in the WHO essential medicines list and human African Trypanosomiasis treatment guidelines by WHO. This drug is used is as first line treatment for first and second stage. It is administered for a period of 10 days within 30 minutes' time after a solid meal is taken and under supervision of qualified trained medical personnel. However, a clinical trial for its application in the treatment of rhodesiense HAT is ongoing (World Health Organization, fact sheets, 2020).

4.0 CONCLUSION

Trypanosomiasis is one of the neglected tropical diseases affecting both animals and humans, causing greater economic loss, effort to discover drugs that could be effective against the parasites, with minimal side effects and resistance is still abortive, as a results, plants-based therapy could have a promising effect against the parasite resistance caused as a result of antigenic variation.

References

Abdulazeez, M.A.; Ibrahim, A.B.; Edibo, Z.Y.; Sidali, J.O., Idris, H.O. (2003) Anti trypanosomal effect of *Peristrophe bicalyculata* extract on *Trypanosoma brucei brucei*-infected rats. *Asian Pac. J. Trop. Biomed.3*: 523–531.

Abenga, J.N.; Lawal, I.A. Implicating roles of animal reservoir host in the resurgence of Gambian trypanosmosis (Sleeping Sickness). *African Journal of Biotechnology* 2005, **4**(2).

Adeiza, A.A.; Maikai, V.A.; Hassan, F.B. Phytochemical screening and evaluation of some medicinal plants for their *in vitro* activities on *Trypanosoma evansi. J. Med. Plants Res.* 2009, *3*, 315–318.

Aderbauer, B., Clausen, P. H., Kershaw, O. and Melzig, M. F. (2008). *In vitro* and *in vivo* trypanocidal effect of lipophilic extracts of medicinal plants from Mali and Burkina Faso. *J. Ethnopharmacol.*; 119: 225 – 231.

Administrative Map of Nigeria—Nations Outline Project. Available online: http://www.nationsonline.org (accessed on 2 February 2015).

Airauhi, L.; Unuigbe, E.I.; Airauchi, O.D. Human sleeping sickness (SS) in Nigeria: Knowledge, attitude and beliefs in a focus in the Abraka belt, Delta of Nigeria. *Afr. J. Clin. Exp. Microbiol.* 2001, *2*, 6–9.

Alawa, J.P.; Jokthan, G.E.; Akut, K. Ethnoveterinary medical practice for ruminants in the sub-humid zone of northern Nigeria. *Prev. Vet. Med.* 2002, *54*, 79–90.

Amaechi, N. Toxicity of antiprotozoan drug diminazene aceturate in rats. *J. Sustain. Agric. Environ.* 2001, *3*, 365–370.

Ameenah, G.; Mohamad, F.M. African flora as potential sources of medicinal plants: Towards the chemotherapy of major parasitic and other infectious diseases—A review. *Jordan J. Biol. Sci.* 2013, *6*, 77–84.

Atawodi, S. E., Bulus, T., Ibraham, S., Ameh, D. A., Nok, A. J., Mamman, M. and Galadima, M. (2003). *In vitro* trypanocidal effect of methanolic extract of some Nigerian Savannah plants. *Afr. J. Biotechol*.; 2: 317 – 321.

Atawodi, S.E.; Bulus, T.; Ibrahim, S.; Ameh, D.A.; Nok, A.J.; Mamman, M.; Galadima, M. *In vitro* trypanocidal effect of methanolic extract of some Nigerian savannah plants. *Afr. J. Biotechnol.* 2003, *2*, 317–321.

Awulu, E.A.; Oniye, S.J.; Adelanwa, M.A. Phytochemical Screening and *in vivo* Antitrypanosomal Activity of Methanol Extracts of *Peristrophe bicalyculata* in Mice Infected with *Trypanosoma evansi*. *Int. J. Sci. Technol.* 2013, *3*, 34–39.

Ayodele, O.M.; Akinyemi, F.; Charles, D.; Kim, P.; Michael, V.T.; Susan, C.W. A Longitudinal Survey of African Animal Trypanosomiasis in Domestic Cattle on the Jos Plateau, Nigeria: Prevalence, Distribution and Risk Factors. *Parasites Vectors* 2013, *6*, 239, doi:10.1186/1756-3305-6-239.

Bauer, B.; Amsler-Delafosse, S.; Kabore, I.; Kamunga, M. Improvement of cattle productivity through rapid alleviation of African management practice in the Agropastoral zone of Yale, Burkina Faso. Animal trypanosomosis by integrated disease. *Trop. Anim. Health Prod.* 1999, *31*, 89–102.

Cragg, G.M.; Newmann, D.J.; Snader, K.M. Natural products in drug discovery and development. *J. Nat. Prod.* 1997, *60*, 52–60.

\\

D'Archivio, S.; Medina, M.; Cosson, A.; Chamond, N.; Rotureau, B.; Minoprio, P. Genetic engineering of *Trypanosoma* (*Dutonella*) *vivax* and *in vitro* differentiation under axenic conditions. *PLoS Negl. Trop. Dis.* 2011, *5*, e1461.

Da Costa, F.B.; de Castro, S.L.; Ferreira, V.F.; de Lacerda, M.V.G.; *et al*. The Potential of Secondary Metabolites from Plants as Drugs or Leads against Protozoan Neglected Diseases Part I. *Curr. Med. Chem.* 2012, *19*, 2128–2175.

Da Costa, F.B.; de Castro, S.L.; Ferreira, V.F.; de Lacerda, M.V.G.; *et al*. The Potential of Secondary Metabolites from Plants as Drugs or Leads against Protozoan

Neglected Diseases Part II. *Curr. Med. Chem.* 2012, *19*, 2176–2228. dietary supplements for glycemic control in diabetes. *Diabetes Care* 2003, *26*, 1277–1294.

Edeghere, H.; Elhassan, E.; Ukah, J.C.A.; Sanda, S.; Ikenga, M.; Audu, G. The scourge of human African trypanosomiasis in Abraka: possible control strategies. *Nig. Soc. Parasitol. Abst.* 1998, *46*, 43.

Fact Sheet N°259: Trypanosomiasis, Human African (Sleeping Sickness); WHO Media Centre: Geneva, Switzerland, 1 June 2013. Available online: http:www.who.int/mediacentre/ factsheets/fs259/en (accessed on 27 February 2014).Gambian trypanosomiasis (Sleeping Sickiness). *Afr. J. Biotechnol.* 2005, *4*, 134–137.

Griffin, L.; Allonby, W.E. The economic effect of trypanosomiasis in sheep and goats at a range research station in Kenya. *Trop. Anim. Health Prod.* 1979, *11*, 127–132.

Guadani, R.; Patel, J.; Prajapati, H.; Mehta, B.; Agrawal, S. Peristrophe bicalculata—A review. *Pharmacogn. J.* 2010, *2*, 39–45.

Hamdan, I.I.; Afifi, F.U. Studies on the *in vitro* and *in vivo* hypoglycemic activities of some medicinal plants used in treatment of diabetes in Jordanian traditional medicine. *J. Ethnopharmacol.* 2004, *93*, 117–121.

Hoet S.; Opperdoes, F.; Brun, R.; Quetin-Leclercq, J. Natural products active against African trypanosomes: A step towards new drugs. *Nat. Prod. Rep.* 2004, *21*, 353–364.

Ibrahim, M.A.; Mohammed, A.; Isah, M.B.; Aliyu, A.B. Anti-trypanosomal activity of African medicinal plants: A review update. *J. Ethnopharmacol.* 2014, *154*, 26–54.

Joshua, R.A.; Magaji, Y.; Kayit, Y.S. Isolation of human serum resistant Trypanozoon from cattle in Nigeria. *Tropenmedizin Parasitol.* 1983, *13*, 201–202.

Idehen C.O., Ishola O.O., Adeyemi I.G., Abengby G., Olaleye O., Aluma AL., Opabunmi R.O., Oba lotto O.B. Prevalence of African Trypanosomosis in cattle and sheep in Bassa Local Government Area of Plateau State, Nigeria. Sokoto Journal of Veterinary Science. 2018, **16**(3): 11-17.

Kaiser, M.; Bray, M.A.; Cal, M.; Trunz, B.B.; Torreele, E.; Brun, R. Antitrypanosomal activity of Fexinidazole, a new oral Nitroimidazole drug candidate for treatment of sleeping sickness. *Antimicrob. Agents Chemother.* 2011, *55*, 5602–5608.

Kabir Ayobami Raheem. A Review of Trypanosmosis-induced Reproductive Dysfunctions in Male Animals. *Journal of Agrosearch*, 2014, **14**(1): 30-38.

Lifongo, L.L.; Simoben, V.C.; Ntie-Kang, F.; Babiaka, B.S.; Judson, N.P. A bioactivity *versus* ethnobotanical survey of medicinal plants from Nigeria, West Africa. *Nat. Prod. Bioprospect.* 2014, *4*, 1–19.

Mahomoodally, M.F.; Gurib-Fakim, A.; Subratty, A.H. Antimicrobial activities and phytochemical profiles of endemic medicinal plants of Mauritius. *Pharm. Biol.* 2005, *43*, 237–242.

Mahomoodally, M.F.; Gurib-Fakim, A.; Subratty, A.H. Screening for alternative antibiotics: An investigation into the antimicrobial activities of medicinal food plants of Mauritius. *J. Food Sci.* 2010, *75*, 173–177.

Malebo, H.M.; Tanja, W.; Cal, M.; Swaleh, S.A.M.; Omolo, M.O.; Hassanali, A.; Séquin, U.; Hamburger, M.; Brun, R.; Ndiege, I.O. Antiplasmodial, anti-trypanosomal, anti-leishmanial and cytotoxicity activity of selected Tanzanian medicinal plants. *Tanzania J. Health Res.* 2009, *11*, 226–233.

Maser, P.; Luscher, A.; Kaminsky, R. Drug transport and drug resistance in African trypanosomes. *Drug Resist. Updates* 2003, *6*, 281–290.

Matthews, H.B.; Lucier, G.W.; Fisher, K.D. Medicinal herbs in the United States: Research needs. *Environ. Health Perspect.* 1999, *107*, 773–778.

Mbaya, A. W., Ibrahim, U. I., God, O. T. and Ladi, S. (2010). Toxicity and potential antitrypanosomal activity of ethanolic extract of *Azadirachta indica* (Meliaceae) stem bark: An *in vivo* and *in vitro* approach using *Trypanosoma brucei*. *J. Ethnopharmacol*; 128: 495 – 400.

Mbaya, A.W.; Ibrahim, U.I. *In vivo* and *in vitro* activities of medicinal plants on haemic and humoral trypanosomes: A review. *Int. J. Pharmacol.* 2011, *7*, 1–11.

Mulumba, K. *Socio Economic and Agricultural Factors in the Research and Control of* Newmann, D.J.; Cragg, G.M. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J. Nat. Prod.* 2012, *75*, 311–335.

Ngozi Justina Nwodo, Akachukwu Ibezim (2015) Anti-Trypanosomal Activity of Nigerian Plants and Their Constituents, *Molecules* **2015**, *20*, 7750-7771; doi:10.3390/molecules20057750 www.mdpi.com/journal/molecules.

Nok, A.J.; Williams, S. *Allium sativum*—Induced death of African Trypanosomes. *Parasitol. Res.* 1996, *82*, 634–637.

Nwodo, N.J.; Brun, R.; Osadebe, P.O. *In vitro* and *in vivo* evaluation of the antitrypanosomal of fraction of *Holarrhena africana*. *J. Ethnopharmacol.* 2007, *113*, 556–559.

Ogbadoyi, E.O.; Abdulganiyu, A.O.; Adama, T.Z.; Okogun, J.J. *In vivo* Trypanocidal activity of *Annona senegalensis*. Pers leaf extract against *T. brucei brucei*. *J. Ethnopharmacol.* 2007, *112*, 85–89.

Ogbunugafor, H. A., Okochi, V. I., Okpuzor, J., Odesanmi, O. S. and Ebigwe, F. J. (2008). The butanol extract of *Mitragyna ciliate* root: Potential as a typanocide. *Int. J. Pharmacol*., 4: 102 – 107.

Ogungbe, I.V.; Setzer, W.N. Comparative Molecular Docking of Antitrypanosomal Natural Products into Multiple *Trypanosoma brucei* Drug Targets. *Molecules* 2009, *14*, 1513–1536.

Peacock, L., Cook, S., Ferris, V., Bailey, M. and Gibson, W., (2012). The life cycle of *Trypanosoma* (*Nannomonas*) *congolense* in the tsetse fly. *Parasit. Vectors*; 5: 109.

Rangasamy, O.; Raoelison, G.; Rakotoniriana, F.E. Screening for anti-infective properties of several medicinal plants of the Mauritians flora. *J. Ethnopharmacol.* 2007, *109*, 331–337.

Ranilla, L.G.; Kwon, Y.I.; Apostolidis, E.; Shetty, K. Phenolic compounds, antioxidant activity and *in vitro* inhibitory potential against key enzymes relevant for hyperglycemia and hypertension of commonly used medicinal plants, herbs and spices in Latin America. *Bioresour. Technol.* 2010, *101*, 4676–4689.

Ravi-Kumar, A.; Ponnusamy, S.; Ravindran, R.; Zinjarde, S.; Bhargava, S. Evaluation of traditional Indian antidiabetic medicinal plants for human pancreatic amylase inhibitory effect *in vitro*. *Evid. Based Complement. Altern. Med.* 2011, *2011*, doi:10.1155/2011/515647.

Sara, H. O. F., Reto, B., Victor, A. and Joelle, Q. L. (2004). *In Vitro* anti trypanosomal activity of ethnopharmacologically selected Beninese plants. *J. Ethnopharmacol*.; 91:37

Schmidt, T.J.; Khalid, S.A.; Romanha, A.J.; Alves, T.M.A.; Biavatti, M.W.; Brun, R.; *Trypanosomiasis*; PAAT Technical and Scientific Series 4; FAO/WHO/IAEA/OAU: Rome, Italy, 3 January 2003.

Yeh, G.Y.; Eisenberg, D.M.; Kaptchuk, T.J.; Phillips, R.S. Systematic review of herbs.