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Use of herbal remedies in the management of sleeping sickness in four northern provinces of Angola☆

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ABSTRACT

Ethnopharmacological relevance: This study reports for the first time on the use of folk medicine to treat sleeping sickness and its symptoms in four endemic provinces in northern Angola. By interviewing both traditional practitioners and confirmed patients, it highlights reasons to recourse to folk medicine, the plant species used for this affection as well as arises awareness about the use of particular plants showing potential risks.

Aim of the study: The aims of this explorative study were three-fold. Firstly, it informed on access to, and use of plant-based medicine as first-choice treatment by infected persons. Secondly, it aimed at collecting comprehensive data from patients and traditional healers on herbal remedies in order to identify plant species used in the management of the disease. Thirdly, it served as contribution for primary indication of potential risk of use associated with the studied plants and their preparation.

Materials and methods: The study was conducted in 4 endemic provinces of Angola, namely Bengo, Zaire, Kwanza Norte and Uíge. We explored the use of herbal remedies by conducting structured and semi-structured interviews within two distinct study populations. The first group comprises 30 patients who had been diagnosed for trypanosomiasis and treated by the reference treatment. The second group included 9 traditional practitioners who had already treated sleeping sickness. The plants that were cited during the interviews were collected during field walks under supervision of a traditional healer, then authenticated and deposited at the National Herbarium in Luanda.

Results: Of the 30 included patients, 12 (40%) had turned to folk medicine in the management of trypanosomiasis and related symptoms. 7 medicinal plants were reported by this group. Considering the key motivation to consult a traditional practitioner, two main factors accounted for half of the cases: “past experience with folk medicine” and “family habit”. Out of 9 traditional practitioners’ interviewees, 26 medicinal plants were cited. Roots and leaves were the most used plant parts, and decoction was the common mode of preparation. Evidence for antitrypanosomal activity in the scientific literature was found for 56% (17 of 30) of the identified plant species. The most cited plant was *Crossopteryx febrifuga* (UR = 6). Some of the cited plants, as for example *Aristolochia gigantea*, raised concern about potential toxicity.

Conclusions: With 40% of infected persons having turned first to folk medicine before consulting a medical doctor, this explorative study points out that plant-based medicines play an important role in local dynamics of health care. It highlights the need for primary assessment of potential risk of use related to the herbal recipes, and for reporting it to the concerned population. This first ethnobotanical study on trypanosomiasis in endemic provinces of Angola provides information on 30 plants, of which some had been identified as promising for

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further pharmacological research. Our results provide a first step towards the validation and valorization of Angolan herbal remedies for sleeping sickness.

1. Introduction

The extensive use of folk medicine (FM) in Sub-Saharan Africa, composed mainly of medicinal plants, has been argued to be linked to cultural and economic reasons. The accessibility and availability of qualified physicians is limited, with counts of only one medical doctor for 40′000 persons (Abdullahi, 2011). This is why WHO encourages African member states to promote and integrate validated traditional practices in their health system (WHO, 2013). In Angola, more than seventy percent[2] of the population uses herbal medicine to treat various medical affections, including parasitic infections.

Human African Trypanosomiasis (HAT) is a protozoan Neglected Tropical Disease (NTD) transmitted by tsetse flies (*Glossina* spp.). It is caused by two different subspecies of *Trypanosoma brucei*: *T. b. gambiense* causes chronic infection and is prevalent in west and central Africa, while *T. b. rhodensiense* causes a more acute infection in eastern Africa. Both forms of the disease are fatal if untreated. At the time of the study, the reported number of new cases in Angola was 35 for 2014 and 34 for 2015. The standard medical treatment uses five different drugs, depending on the disease stage: pentamidine and suramin are used in the first, hemolymphatic stage; melarsoprol and nifurtimox-eflornithine combination therapy (NECT) in the second stage, the cerebral stage (Brun et al., 2010; WHO, 2019). Fexinidazole is a new drug, the first-ever oral treatment for all stages of *T. b. gambiense* HAT that successfully passed clinical trials and was recently endorsed by the European Medicines Agency (Deeks, 2019; Mesu et al., 2018). This new and easy-to-apply drug for both stages of the disease constitutes a huge leap forward in the treatment of sleeping sickness and is a step forward to the elimination of HAT. Acoziborole is an additional oral treatment in the development phase meant to be given as a single dose treatment for both stages (Baker and Welburn, 2018). All drugs are donated by the manufacturers, and WHO guarantees free-of-charge distribution (Büscher et al., 2017). There is no vaccine against trypanosome infection, and chemoprophylaxis is not used because of the toxicity of the available drugs and the low incidence of infection.

The geographical distribution of HAT is highly contingent upon environmental conditions for the *Glossina* flies. Sleeping sickness is found in the northwestern part of Angola and is prevalent in seven provinces out of eighteen (Truc et al., 2011). Bengo, Kwanza Norte, Uíge and Zaire are the four highest risk areas and 5.8 million people are at risk (Simarro et al., 2015). We know that the disease mainly affects remote rural communities, where health infrastructure is basic and its accessibility complicated (Franco et al., 2014). Moreover, the number of reported cases relies on systematic control activities and national surveillance program. The current economic recession that impacted the stability of the national economy in Angola since 2015, affected the efficiency of screening activities [private communication/medical team of ICCT, 2016]. As a consequence, a certain number of cases are undetected and untreated by the surveillance programs, leading to a gap between the number of cases declared and the number of actual cases (Truc et al., 2011). In absence of vaccine and chemoprophylaxis, the infection is mainly controlled through case detection and treatment. Thus, HAT can upsurge, if control measures should be relaxed, for example in the context of conflict or socio-political instability (Berrang-Ford et al., 2011).

In such context, the investigation of herbal remedies as a natural affordable and accessible resource is of high relevance. The scientific validation of an herbal preparation, through its botanical and pharmacological assessment, guarantees a safe and effective use of the remedy and contributes in that sense to strengthening of the health system. Thus, for hard-to reach communities much exposed to the disease with difficult access to healthcare, the use of a “validated” recipe in the management of sleeping sickness would be a complementary response for the improvement of health conditions and a mean of valorizing local medicinal knowledge.

This prompts us to investigate whether or not folk medicine is used to treat sleeping sickness, and to assess the potential use of herbal medicine in case of infection by this parasitic disease. Therefore, the following research questions were addressed: (i) among the infected and treated persons, how many had turned to FM before consulting a medical doctor? (ii) what are the therapeutic options followed by the patients infected with trypanosomiasis? (iii) what are the botanical species used in the management of sleeping sickness? (iv) are there any potential risks of use associated with the studied plant species?

The last decades have witnessed a range of investigations reporting antitrypanosomal activity of traditionally used African medicinal plants, and several reviews compiling the major results have been published (Gehrig and Efferth, 2008; Gurib-Fakim and Mahomoodally, 2013; Ibrahim et al., 2014; J Schmidt et al., 2012; Mahomoodally, 2013; Mwangi et al., 2017; Nwodo, N. et al., 2015a; Ogungbe and Setzer, 2016; Simoben et al., 2018). Concerning Angola, a thorough description of the use of medicinal plants in central and western parts of Angola was provided by Eric Bossard (1996). A few ethnobotanical studies described the knowledge of traditional use of plants in Angola (Göhre et al., 2016; Heinze et al., 2017; Lautenschläger, 2014; Lautenschläger et al., 2018; Leyens and Lobin, 2009; Urso et al., 2016; Van Dúnem, 1994; Videira et al., 2011). Da Costa and Pedro (Da Costa, 2013) summarized in their book general ethnomedical information about medicinal plants commonly used in this country. All the above mentioned works focused on traditional knowledge. Apart from a recent ethnopharmacological study on anti-inflammatory effect of medicinal plants from Angola (Pompermaier et al., 2018), there has not been a previous ethnopharmacological study reporting the use of herbal remedies to treat a parasitic disease in Angola.Due to the paucity of ethnopharmacological scientific data on HAT in Angola, we conducted an explorative study among infected and already treated persons (patients) as well as among traditional practitioners in order to gather valuable primary information about the use of herbal medicine as first-line treatment for HAT.

Our ethnopharmacological explorative study aims at (i) reporting the use of folk medicine to treat sleeping sickness and related symptoms in endemic provinces of Angola, (ii) documenting the used medicinal plant species (iii) identifying potential risks related to certain plant species and their preparation.

2. Materials and methods

2.1. Study area

Angola counts 18 provinces, 162 municipalities and 559 communes. This explorative study took place in the four highest-risk provinces of Angola, namely Bengo (green), Kwanza Norte (mustard), Uíge (yellow) and Zaire (orange) (Fig. 1). Bengo (highlighted in green) and Kwanza norte (highlighted in mustard) are the two least populated provinces of Angola. Two ethnolinguistic groups can be found among these four provinces. The first group, namely Quicongo (Kikongo ou Conguês) is composed of Bakongo people and covers the provinces of Zaire and

[2] Percentage given at the 1st *National Conference of Traditional Medicine and Complementary Practices* held in Luanda in August 2012.

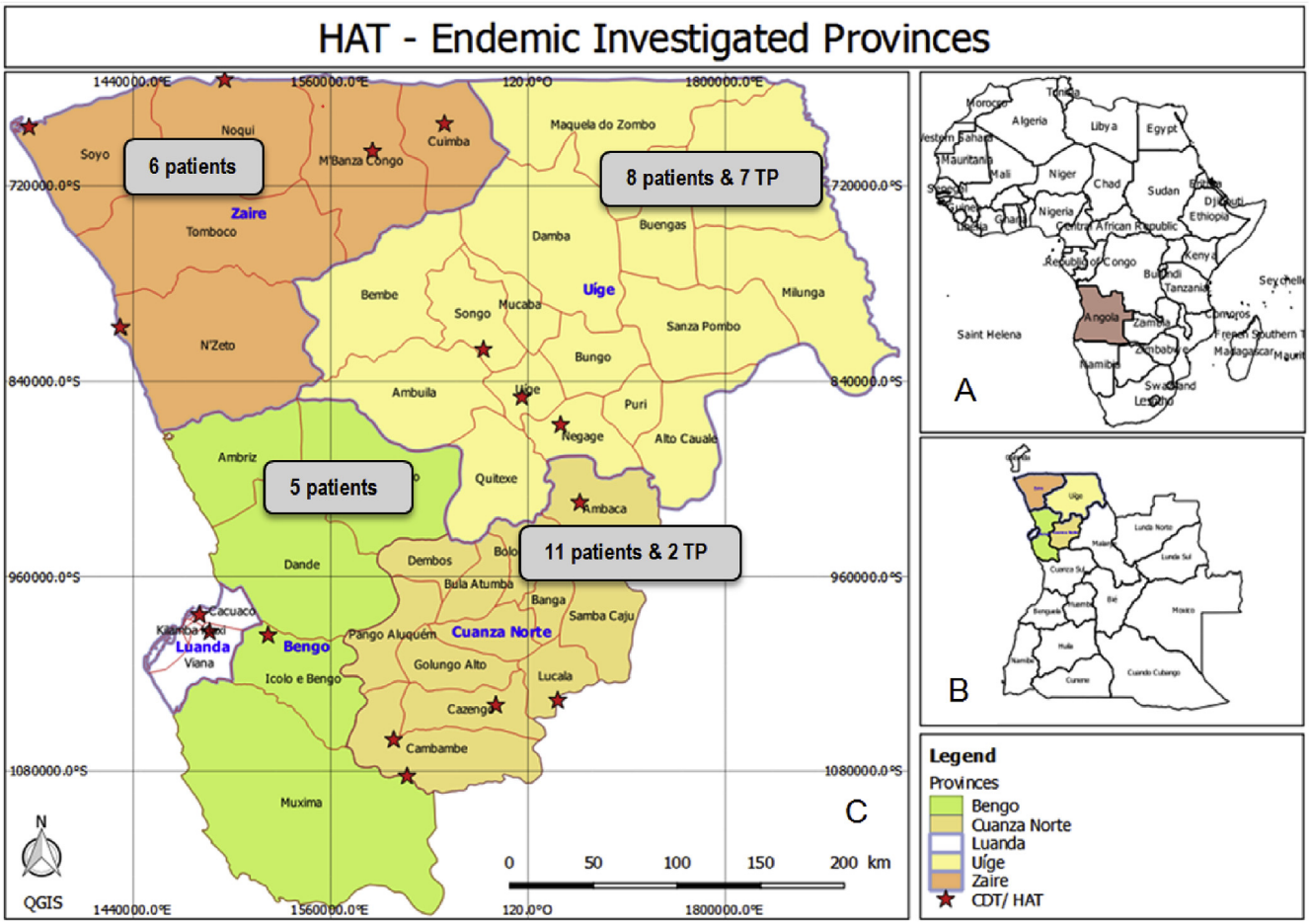

Fig. 1. Geographical location of Angola in Africa and the four studied provinces in colors.
Legend: CDT/HAT- Trypanosomiasis Diagnostic and Treatment Center
A: Angola is located in the southern part of Africa. B: the four northern endemic provinces that were inquired. C: Investigated provinces and the number of respondents per provinces. Province of Zaire (orange)/
6 patients were interviewed; province of Uíge (yellow)/8 patients interviewed and 7 traditional practitioners (TP); province of Bengo (green)/5 patients interviewed/ province of Cuanza Norte (mustard)/11 patients interviewed and 2 traditional practitioners (TP).

Uíge and a part of Kwanza-Norte. They mainly speak kikongo, one of the national language. The second ethnolinguistic group is represented by the Quimbundo (Kimbundu ou Tyumbundu). It is composed of the Mbundu people and includes the provinces of Bengo and part of Kwanza-Norte. Their language is the kimbundu, another national language.

Municipalities covered by interviews of patients and traditional practitioners were: Dande, Ambriz for Bengo province; M'Banza Kongo for Zaire province; Uíge, Songo, Makela do Zombo, Beu, Bungo for Uíge province; and Cazengo, Banga, Dondo for Kwanza Norte province. Fig. 1 shows the number of participants interviewed per province.

At the time of the study, 15 fixed health centers were responsible for diagnostics and treatment of HAT in the 4 inquired provinces (location highlighted by a red star/Fig. 1), covering approximately 150 000 km^2 and a total population of 2′877′573. The detection of new cases relies on active screening by mobile teams and passive screening in the fixed health centers. In 2014, Angola officially registered 36 new cases, followed by 35 in 2015 (WHO, 2016) and 18 in 2017.

Except in the urban and peri-urban areas, the surveyed area is mostly rural, characterized by activities like farming, hunting and fishing. The rural environment offers suitable conditions for the development of tsetse flies and human-tsetse contact. The traditional practitioners mainly originated from Uíge province. This reflects a strong presence of FOMETRA in that province, one of the two most important organizations of traditional practitioners at national level. In Uíge FOMETRA counts 14′201 traditional practitioner members. In comparison, Bengo counts 2703 traditional practitioners, Zaire 1744 and Cuanza Norte 1936 (approval by [Avô] Kitoko Maiavanga, coordinator of CATEMETA, personal communication, 2017

2.2. Study population

There were two distinct study populations, patients and traditional practitioners. The patients' population consisted of participants treated for trypanosomiasis within 2014 and 2015 by the *Instituto de Combate e Controlo das Tripanossomíases* (ICCT) and its provincial medical centers. Out of 60 patients, 30 were interviewed, the remaining half consisting of patients who could not be reached or had to be excluded because they were less than 18 years old. The enclosed patients were under follow-up treatment, which allowed us to work with clinically confirmed and treated cases, a crucial point for medical and ethical reasons. Access to medical records helped us to geolocate the participants. This design enabled us to investigate whether the patients had turned first to folk medicine, before consulting a medical doctor, and by consequence to assess the use of herbal medicine for clinically confirmed cases.

The specialists' population was composed of 9 traditional practitioners originating either from Uíge Province or Kwanza Norte. They are members of *FOMETRA* or *CONMENTA*, the two most important national healers' associations. The traditional practitioners were

selected first on recommendation of the scientific leader of FOMETRA and the correspondent provincial director, based on their reputation in the treatment of sleeping sickness. Independent advice was obtained from the municipal representative of the association, who, as a local contact, was foremost aware of the competence of the traditional practitioners regarding HAT. The selection was also influenced by the willingness of traditional practitioners to participate in the study. Finally, only 9 traditional practitioners have fulfilled the inclusion criteria (see supplementary file S1, study protocol).

2.3. Data collection

Data were collected over a 5-month period, from October 2016 to March 2017, covering about 25 different localities distributed in 4 provinces. The interviews were led in Portuguese and, when needed, the questions were translated orally to local dialect (Kikongo or Kimbundu) by a field assistant that was either a member of the group or a translator. Two different questionnaires were used (see supplementary data S2 and S3), both of which included general sociodemographic features like age, sex, location, level of education and spoken language. Local name of disease, symptoms of disease, cause of disease and disease transmission were also asked to both groups of respondents.

The interview sessions with traditional practitioners were realized in the privacy of their home and lasted for an average of 1 h. The questionnaire involved a set of questions including category of healer, local name of plant, mode of preparation, mode of administration, precaution of use, focusing on the herbal treatments used as well as their representation and the healer's understanding of sleeping sickness. A second session was organized to collect the plant material during field walks under guidance of the respondent or of the local representative traditional practitioner.

Also the patients' inquiries were conducted at their home and included questions about distance to next health center, type of first choice treatment, key motivation to use FM, frequency of use of FM. Some of the mentioned plants were also collected during field walks.

Before each interview voluntary participation was previously confirmed by a written informed consent.

Ethical approval for the study (study protocol and the informed consent form) was obtained by the Swiss *Ethikkommission Nordwest-und Zentralschweiz* (EKNZ BASEC Req-2016_00403) and the Angolan *Comité da Ética ad hoc* (Ministerial decree of 14.09.2016, ofício N°2469/GAB.MIN/MS/2016).

2.4. Plant material

The plant specimen described by specialists and/or by patients were collected during field walks in Uíge and Kwanza Norte provinces (highlighted in yellow & mustard/Fig. 1). Plant sampling was carried out in provinces of Uíge and Kwanza Norte. The collecting area extends from 6°01.173′ and 9°19.867′ southern latitude and 14°49.401′ and 25°23.914' longitude. The main part of sampling took place in municipalities of Uíge, Maquela do Zombo, Damba of Uíge province and Kazengo and Kambambe of Kwanza Norte province.

The plants were collected based on the vernacular name cited by the informant. The herbarium specimen was photographed and collected during field work, carefully pressed and dried, and stored at the National Botanical Center in Luanda, which is part of the Faculty of Sciences at University of Agostinho Neto. A first determination was done with assistance of specialized botanists. Authentication was then carried out at the National Botanical Center in Luanda. For identification of plants, we determined the family, genus and species by (i) comparing with existing herbarium specimens (ii) consulting the Herbarium database of the National Botanical Center and specialized databases, including *Tropicos*, the *African Plant Database*, *The Plant List,* (iii) by referring to floristic references (Figueiredo, 2008; Gossweiler, 1953).

2.5. Data analysis

Qualitative data were analyzed with MAXQDA software. Fisher's exact test and the Wilcoxon rank sum test were used to compare categorical and numerical variables, respectively, between the FM- and PM-patients. Collected plant data were treated with open-source QuantumGIS 2.14.8-Essen software. To quantify the collected ethnobotanical data, we recorded the use report (UR). Every plant use reported in a herbal recipe was considered as a separate record and counted as one use report (Lardos and Heinrich, 2013). If a plant species was mentioned several times in different recipes, the use report was accordingly counted.

The online bibliographic databases *Pubmed*, *Science direct*, and *Google scholar* were consulted for studies on antitrypanosomal activity of the identified plant species. The literature search was conducted by using the botanical name (and its synonyms) of the studied species in combination (Boolean AND) with the following keywords: sleeping sickness, trypanosomiasis, antitrypanosomal activity, folk use, traditional use, ethnopharmacological use, ethnomedical use, and ethnobotanical use. Further articles were included by tracking the cited references. Studies that explicitly reported on plant extract tested for *in vitro* and/or *in vivo* antitrypanosomal activity were selected.

In order to estimate potential risks of toxicity for each species, online bibliographic databases such as *Pubmed* and *Science direct* were consulted.

3. Results

3.1. The use of folk medicine in the case of sleeping sickness

3.1.1. Local nosology

Sleeping sickness is known in Portuguese, the official language in Angola, as "doença do sono" and is frequently referred to by a local

Table 1
Number of patients with sleeping sickness according to first choice of treatment.

Type of first treatment	Provinces inquired				Total number of patients	Percentage (%)	Total percentage (%)
	Bengo	Zaire	Kwanza norte	Uíge			
Biomedical reference treatment (active[a])	1	0	2	1	**18**	13.3%	60.0%
Biomedical reference treatment (passive[a])	1	4	6	3		46.7%	
Herbal treatment from traditional healer/herbalist ("curandeiro")	1	1	2	3	**12**	23.3%	**40.0%**
Herbal treatment from sorcerer ("kimbandeiro")	0	1	0	1		6.7%	
Herbal self-treatment ("caseiro")	1	0	1	0		6.7%	
Other[b]	1	0	0	0		3.3%	
Total	5	6	11	8	**30**	100.0%	100.0%

The patients are distributed according to their first treatment choice and the province they originate. Legend: [a] type of screening; [b] herbal treatment given by a Chinese medical center located in Luanda.

Table 2
Plants used by patients or/and traditional practitioners in the management of trypanosomiasis.

Plant N°	Scientific name/local name[a]	Botanical family	Collection number	Part used	Modes of preparation	Usage (route, mode of administration)	Informant group[sp & nsp]	Use reports (UR)
1	*Nymphaea lotus* L./Longa dia simbi	Nymphaeaceae	2513	Wp	decoction	oral, drink	Sp	1
2	*Palisota schweinfurthii C.B.Clarke*/Mabunda bunda	Commelinaceae	894	L	decoction, maceration	oral, drink	Sp	3
				L	maceration	topical, facial wash		
				L	maceration[m2]	oral, drink & dermal, body massage		
3	*Entada abyssinica A.Rich.*/Nsofi	Fabaceae	3468	R	decoction or maceration	anal, clyster & oral, drink	Sp	2
				R	direct use, grated fresh roots	topical, nasal drops		
4	*Brillantaisia owariensis P.beauv.*/Malemba lemba	Acanthaceae	7925	L	maceration	oral, drink	Sp& nsp	2
5	*Sarcocephalus latifolius (Sm.)E.A.Bruce*/Nlolo	Rubiaceae	8231	R	decoction	oral, drink	Sp	1
6	*Fleroya stipulosa (DC.) Y.F. Deng*[a]/Nlongo	Rubiaceae	8227	T	decoction	oral, drink	Sp	1
7	*Crossopteryx febrifuga (Afzel.ex G.Don) Benth*/Mvala	Rubiaceae	8212	L	direct use, crushed fresh leaves	topical, ocular & nasal drops	Sp& nsp	6
				R	decoction[m1]	oral, drink		
				R	decoction or maceration,	oral, drink & anal, clyster		
8	*Trilepisium madagascariense DC.*/Nsiekeni or nzeke nzeke	Moraceae	9795	R, Tb	decoction	oral, drink	Sp	1
9	*Steganotaenia araliacea Hochst.*/Kula mvumbi or Kula mpinga	Apiaceae	6116	R	infusion	oral, drink	Sp	1
10	*Daniellia alsteeniana P.A.Duvign*/Nlomba	Fabaceae	3512	T	decoction	oral, drink & facial washing	Sp	2
11	***Carica papaya* L./Papaya[Pt]	Caricaceae	5377	R	decoction[m1]	oral, drink	Sp	1
12	***Nicotiana tabacum* L./Fumu or Tobaco[Pt]	Solanaceae	7434	L	direct use, crushed fresh leaves	topical, ocular & nasal drops	Sp	1
13	*Vitex madiensis Oliv.*/Nfilu	Lamiaceae	7186	L	direct use, crushed fresh leaves mixed with palm wine "maruvo"	topical, ocular drops	Sp	3
				L	decoction	oral, drink		
14	*Momordica charantia* L./Lumbuzu	Cucurbitaceae	8591	Ap	decoction[m1]	oral, drink	Sp	3
				L	maceration[m2]	oral, drink & dermal, body massage		
				L	decoction	oral, drink		
15	***Capsicum frutescens* L./Ndungu	Solanaceae	7404	S	direct intake	oral, chewing	Sp & nsp	2
				L	decoction[m3]	oral, drink		
				L	direct use, crushed fresh leaves	topical, cranial cataplasm		
16	*Securidaca longipedunculata Fresen.*/Nsunda	Polygalaceae	4275	R	maceration[m2]	oral, drink & dermal, body massage	Sp	2
17	*Cymbopogon densiflorus (Steud.) Stapf*/Lusangu sangu	Poaceae	134	F, Fl	decoction[m3]	oral, drink	Sp	1
18	*Sansevieria hyacinthoides (L.) Druce*/Espada de S.Jorge	Asparagaceae	1110	L, R	direct use, grated fresh leaves & roots	dermal, body massage	Sp	1
19	*Aristolochia gigantea Mart.*/Cipó mil	Aristolochiaceae	2174	R	infusion	oral, drink	Sp	1
20	*Cascabela thevetia (L.) Lippold*/Tevetive or Kizuza[Kim]	Apocynaceae	4105/A	Fr, L	infusion	oral, drink	Sp	1
21	*Smilax anceps Willd.*/Mbuakaiona[Kim] or Lunzila nzila	Smilacaceae	1151	R	infusion[m4]	oral, drink	Sp	2
22	*Aframomum angustifolium (Sonn.) K.Schum.*/Ginguenga	Zingiberaceae	1343	Rh, Fr	infusion	oral, drink	Sp	1
23	***Senna occidentalis (L.) Link*/Dinioka nioka or Kikunde[Kim]	Fabaceae	3536	R	infusion[m4]	oral, drink	Sp	1
24	*Monodora myristica (Gaertn.) Dunal*/Jimpeve	Annonaceae	2733	L	direct application, crushed fresh leaves	dermal, cranial cataplasm	nsp	1
25	*Ocimum gratissimum* L./Mansusu nsusu or Dinsusu nsusu or mansudi nsudi or matsudi tsudi	Lamiaceae	7366	L	decoction	oral, drink	nsp	2
				L, A	direct application	dermal, skin vaccine		
26	*Xylopia aethiopica (Dunal) A. Rich*/Nkwua kwa	Annonaceae	2717	NI	NI	NI	nsp	1
27	*Chromolaena odorata (L.) R.M.King & h.Rob.*/Mubulututu	Compositae	8816	L	direct consumption, crushed dried leaves	oral, chewing	nsp	1
28	***Bryophyllum pinnatum (Lam.) Oken.*/Luyika yika	Crassulaceae	3166	L	direct use, crushed fresh leaves	dermal, body massage	Sp	1
29	*Gardenia ternifolia Schumach. & Thonn.*/Lemba nzau	Rubiaceae	8285	Fr	decoction	oral, drink	Sp	1
30	*Azadirachta indica A.Juss.*/Cura tudo [Pt]	Meliaceae	4176	L	direct use, crushed fresh leaves	dermal, body massage	Sp	1

Legend: Wp: whole plant, L: leaves, R: roots, T: trunk, Ap: aerial part, Tb: trunk bark, Rb: root bark, S: seeds, Fl: flowers, Fr: fruits; Rh: rhizome, A: ashes. Plants were sometimes used in a mixture: m_1: Herbal mixture made of C. febrifuga, S. latifolius, M. charantia, F. stipulosa, C. papaya/m_2: Herbal mixture made of P. schweinfurthii, M. charantia, S. longipedunculata/m_3: Herbal mixture made of C. frutescens and C. densiflorus/m_4: Herbal mixture made of S. anceps, S. occidentalis, Kavula mazumba, Mutamundele, Takange. Informant group: sp = specialist, nsp = patient; NI: information not indicated; conservation status according to IUCN red List: vulnerable[a].

[a] Local name are systematically given in Kikongo; when another language is used, it referred either to Kim: Kimbundu or Pt: Portuguese. ** naturalized plants species.

name according to the spoken ethnic language. In the four inquired provinces, two main national languages are used, namely Kimbundu and Kikongo as well as dialects that are particular to a region. As such, sleeping sickness has different appellations for example the term "Manimba", literally translated as "sleep", is used in dialect of Kikongo spoken in the province of Uíge or "Tonji", translated to "sleep", is a local appellation used in Kimbundu dialect spoken in the province of Bengo. These different designations of the illness in local tongues refer to the most characteristic symptom of the disease which is sleepiness.

3.1.2. The users of folk medicine

The selected 30 patients had all been diagnosed with T. b. gambiense HAT (g-HAT) and received modern chemotherapeutic treatment. 12 (40%) of them admitted to having previously received traditional remedies. Thus, two distinct groups resulted from the inquiry: the folk medicine (FM) patients group (n = 12) who had first consulted a traditional practitioner, and the professional medicine (PM) patients group (n = 18) who had directly turned to a biomedical doctor (see Table 1).

In more than half of the cases (7 out of 12), the herbal treatment was provided by a traditional healer ("curandeiro"), whereas two patients consulted a sorcerer ("kimbandeiro") and two others used a self-herbal treatment ("caseiro"). In one case, the herbal remedy was provided by a Chinese doctor from a Chinese medical center.

When comparing the distribution of socio-demographic and health-care related determinants (age, gender, education level, primary occupation, distance to next health center, previous experience with folk medicine and economic level) between the two groups of patients, we found no sizable differences according to age, gender or household economic level. Among all the determinants studied, previous experience with folk medicine was the only one that significantly impacted the recourse of herbal remedies in the management of sleeping sickness: 11 patients (of 12) of FM patients group had already used folk medicine ($p = 0.002$) compared to 6 patients (of 18) of the PM group. The symptomatology and the family habit were two key motivations that patients evocated for consulting a traditional practitioner. Concerning the symptoms, severe and long-lasting neuropsychiatric disorders like behavioral change and somnolence were mentioned as characteristic signs of illness that prompt the patients to turn to a traditional practitioner. Added to that, the influence of family habit in health-seeking behavior played an important role in the therapeutic option. Concerning the 12 patients' satisfaction with the herbal treatment, 3 were satisfied mentioning that *"it helped"* or *"it relieved*, but it didn't cure. The remaining 9 patients were not satisfied reporting that the herbal preparation had no effect or that traditional practices were not trustful based either on disappointing experience or negative perception of the traditional practitioner. The patients provided two main explanations for the cause of the disease, either a supernatural origin or a pathogenic agent. No significant difference related to local etiology was observed between the FM group and the PM group.

3.1.3. The providers of folk medicine

Even though there are 80 times more traditional healers than doctors in Angola, only few traditional practitioners treat it. We had access to 9 practitioners known for having already treated sleeping sickness, none of which claimed to be a specialist for this indication. The most experienced traditional practitioner, whose experience referred to epidemic periods, had treated more than 20 patients, whereas the others had treated only a few cases. The main signs on which they rely to identify the disease are sleepiness, behavioral change and a blurred vision. All these clinical features evocated by the traditional practitioners indicate mainly symptoms of the second phase of the disease. On the contrary, first phase symptoms are unspecific, as for example, chronic or intermittent fever, headache, itching and lymphadenopathy. In contrary to the patients, all traditional practitioners had a particular idea about the illness etiology and they mainly attributed sleeping sickness to the bite of a fly or a mosquito or even spiritual influences. They generally don't know that it is lethal when untreated. Finally, in case of treatment failure, they mostly either changed their herbal prescriptions or recommended another specialist. In two cases, the patient could optionally be redirected to a health center. One spiritualist attributed treatment failure to sorcery intervention.

3.2. The variety of plants used in the treatment of trypanosomiasis

A total of 37 plants was recorded of which 30 could be identified (see Table 2); 7 were presently not followed up because of lack of complete specimen.The plants name has been checked with http://www.theplantlist.org accessed on 1st of June 2019.

Of the 30 identified plants, 23 were only mentioned by the traditional practitioners, 4 by patients and 3 by both groups (see Table 2/see column "informant group" - Sp & nsp). 6 patients of the FM group, could name the plants in the herbal mixture used. As evidence, the two patients that had referred to self-medication, could easily name (vernacular name) and describe the plants used in the herbal remedy. 26 plants were mentioned by 9 traditional practitioners, corresponding to 9 different treatments made of 23 different herbal recipes. Each recipe specifically targets a symptom. The herbal treatments were made of one to three recipes. Most recipes (16 of 23) were made of 1 plant, and only two recipes were composed of 5 different plants. Table 3 shows an example of herbal treatment made of 3 herbal recipes.

The most cited mode of preparation was decoction in boiling water for about 15 min. Less frequently mentioned were macerations, infusions and crushed fresh plant material for direct application or intake, as for example cranial cataplasm or ophthalmic drops. The most represented family was the *Rubiaceae* with four different species mentioned, out of which *Crossopteryx febrifuga* was the most cited plant; it was included in 6 different recipes and was used by specialists as well as by patients. *Vitex madiensis*, *Momordica charantia* and *Palisota schweinfurthii* were equally cited (UR = 3, see Table 2) exclusively from specialists. Leaves and underground organs (root, rhizome) were the most commonly used plant parts. Except for one traditional practitioner, who claimed that *Trilepisium madagascariense* and *Daniellia alsteeniana* were specific for the treatment of HAT, all other specialists mentioned at least one other indication the plant was used for, like for example malaria, diabetes, convulsions or infections. None of the studied plants is endemic and three species are naturalized (see Table 2, indicated by

Table 3
Example of an herbal treatment made of 3 different recipes.

Recipe 1: nasal drops	Recipe 2: drink	Recipe 3: drink
Entada abyssinica/R	Crossopteryx febrifuga/L Vitex madiensis/L	Sarcocephalus latifolius/R Momordica charantia/R Fleroya stipulosa/T Crossopteryx febrifuga/R
Mode of preparation. Direct use of crushed fresh root **Mode of administration:** nasal droops **Use:** alleviate headache	**Mode of preparation:** decoction **Mode of administration:** drink **Use:** against somnolence & eyes trouble	**Mode of preparation:** decoction **Mode of administration:** drink **Use:** "antibiotic"

Plant parts used: R: root, L: leaves, T: trunk.

double asterisk**). 4 plants species, *Azadirachta indica, Bryophyllum pinnatum, Daniellia alsteeniana,* and *Gardenia ternifolia*, were claimed to be used as prevention either as a repellent by rubbing crushed fresh leaves on the skin or in the form of oral intake as a fortifying drink. In terms of treatment, only one traditional practitioner differentiated the plants to be used according to disease stage: *Steganotaenia araliacea* was claimed to be used specifically in early phase against fever, headache, and great tiredness whereas *Palisota schweinfurthii* in advanced phase against behavioral change and somnolence.

3.3. Precaution of use, potential risk of use and recommendations

In order to identify potential risks of use associated with the herbal preparations described in this work, we inquired the users of FM (14 patients: 12 who chose FM as first treatment and 2 who turned to FM as second treatment) as well as the specialists' group, to find out if there was any precaution to be taken, when following the herbal treatment and if so, what these were.

All traditional practitioners except one listed at least one precaution of use. The three most cited were "no alcohol", "not for pregnant woman" and "with dietary restrictions" (see Table 4).

Less than half of the users (6 of 14) mentioned a precaution of use. Except for one patient that referred to dietary restrictions, all others precautions mentioned by the users could not be correlated to the ones stated by the specialists, e.g. to reduce physical effort during treatment period. Past experience and own knowledge also contribute to raise awareness of the risk of use of herbal preparations. So, for instance, one patient refused to take the plant-based prescription claiming that the recommended herbal preparation would give itching and affect the stomach.

4. Discussion

4.1. Use of folk medicine and health-seeking behavior in case of g-HAT

All interviewed patients underwent follow-up treatment in line with the Angolan National Sleeping Sickness Control Programs (NSSCPs). Our study revealed that 40 percent of the inquired patients had used herbal drugs before consulting a biomedical practitioner. This number appears high when we consider that the reference treatment is provided for free to HAT patients in the reference health centers. Comparable results were found in Senegal in a study led among tuberculosis patients (n = 117), of whom 41 percent made use of herbal medicine before reference treatment (Diop et al., 2018). This study shows that plant-based medicines play an important role in local processes of health care in Angola. With respect to this, Göhre et al. (2016) found in their regional ethnobotanical assessment in the province of Uíge that out of 498 different use-reports for 122 plants, 72.1 percent referred to a medical use-reports. These findings provide ample evidence that folk medicine plays an important role in the current primary health care in Angola, even though the country has not yet approved a national policy on Traditional Medicine (WHO, 2005). Thus the non-approved status of folk medicine and its hidden space may push users not to disclose its use in front of biomedical staff, leading to an underestimation of its importance.

When we look at the key motivation of the FM group to consult a traditional practitioner as first line treatment, two reasons played a crucial role: "past experience with FM"and "family habits". Dos Santos et al. (2012) in his master thesis conducted an explorative study in the pediatric hospital of Lubango (capital of Huila province in southern Angola) and analyzed the use of traditional medicine as the parents' response to their children's disease (Santos, 2012). He found that 25 percent of the interviewed families were motivated to seek for a traditional treatment when based upon recommendation of the neighborhood or family habit. A study conducted in Kenya provided similar results, where reasons associated with the use of herbal medicine by patients in herbal clinics were analyzed (Ondicho et al., 2015). Their results highlighted the importance of the impact of family, friends and neighbors on health care practices for herbal medicine. This underlines the meaningfulness of family tradition, community members and habits on health seeking behavior for herbal medicine.

Though our findings show a significant adherence to folk medicine among sleeping sickness patients (40 percent), the perceived effectiveness of the herbal treatment appeared to be low, with only 3 patients of 12 reporting satisfaction about improvement or alleviation of the symptoms. This could suggest that patients might turn to folk medicine more due to social habits or cultural aspects, like disclosing the cause of the disease, than as specific HAT-related health seeking practice. Nevertheless, being knowledgeable about medicinal plants appears to be an important reason associated with the use of folk medicine: More than half of our respondents were aware about the plant parts to be used, their preparation and partially about the name of the plants. This result is consistent with other studies (Fakeye et al., 2009), where the patients' knowledge and notion of medicinal plants influenced the use of herbal medicine.

Sleeping sickness is a chronifying disease that evolves in two phases. Stage 1 is the haemolymphatic stage whose leading signs are non-specific as for example chronic and intermittent fever, headache, pruritus and lymphadenopathy. Stage 1 can even remain asymptomatic (Büscher et al., 2017). As the symptoms are unspecific, the patients often do not feel the need to go for a health check. Stage 2 is the meningoencephalitic stage that is characterized by the invasion of the nervous system by trypanosomes and marked by sleep disturbances and neuropsychiatric disorders. The specificity and severity of the symptoms in stage 2 push patients to seek treatment. Unfortunately, the second stage treatment presents frequent adverse reactions that can be severe or even life-threatening (Brun et al., 2010). We have observed that HAT symptoms – evocated by patients and traditional practitioners – referred mainly to the second phase of this disease and were related to active health seeking. This finding is in line with a previous study conducted by Mpanya et al. among local population in Kasai-Oriental (Democratic Republic of Congo), where patients mainly seek for assistance in the late stage of the disease (Mpanya et al., 2012). Moreover, it shows that the included traditional practitioners were aware of the signs of illness that correspond to the late stage. This suggests that the management of g-HAT in Angola only starts after the outbreak of aggravating and apparent symptoms of the second phase, emphasizing the challenging situation traditional practitioners are confronted with.

The unspecific symptomatology in the early stage combined with neuropsychiatric disorders in the late stage of the disease account for the intricacy of a self-recognized illness. Indeed, the significant proportion of respondents who recourse to folk medicine also reflects that clinical signs of the disease may probably be related at first to a folk illness. Here, a folk illness designates an illness not equivalently associated to a biomedical disease, hence being considered locally as a "*traditional illness*". This local category of sickness is named "*doença tradicional*" ("traditional illness") in Portuguese and refers to a culture-specific understanding of an illness for which biomedical treatment does not help and whose cure is dependent on a "traditional treatment" provided exclusively by a traditional practitioner. For example, the

Table 4
Main precautions of use cited by healers when prescribing herbal remedies.

N°	Precaution of use	Frequency of citation (n = 9)
1	No alcohol	8
2	Not for pregnant woman	6
3	With dietary restrictions	6
4	Restricted prescription for children	2
5	Not with modern treatment	2
6	No sexual activity	1

An herbal remedy can be recommended with several precautions of use.

traditional illness "*cabeça aberta"* that literally means "opened head" is a characterized by strong headache originating from midline along the sagittal suture and whose traditional treatment is made of a plant-based cataplasm applied on the cartilaginous cranial part. This result is comparable to other studies (Ondicho et al., 2015; Stekelenburg et al., 2005), where respondents believe that certain characteristics of a perceived illness are traditionally recognized and categorized to be only cured by herbal medicine or traditional practitioners. Moreover, changes in personality and behavior that may occur in the second phase of sleeping sickness are mental signs that probably play an important role in relating the etiology to supernatural, magical or evil nature, which leads to recourse to a sorcerer (*"kimbandeiro")* or traditional practitioner. We conclude that a persistent non-specific symptomatology in the first stage as well as the prolonged neurological alterations in the second stage of the sickness account for the convolution of the patients' therapeutic itinerary.

The distance to the next reference health center was pointed out to be another limiting reason regarding biomedical treatment. In its g-HAT endemic provinces, Angola is equipped with 17 fixed health facilities (see Fig. 1/red stars), distributed between 7 provinces (Luanda (1), Bengo (1), Zaire (5), Uíge (3), Kwanza Norte (5), Kwanza Sul (1), and Malanje (1)) for diagnosis (with the Card Agglutination Test for Trypanosomiasis [CATT tests]) and delivering reference treatment. In the case of the northern province Uíge, whose area covers 58′698 km^2 and whose population counts 1.5 million (Ceita, 2016) there are only three health centers that can meet the needs of infected patients (at the time of the study). The distance for rural communities to one of these three reference centers lies between a travel-time of 1–3 h (Simarro et al., 2014), which causes considerable travel, accommodation and food expenses. Even though active finding strategies are run punctually in inland areas, the difficult accessibility to the reference treatment sites may have contributed to the use of FM in the management of sleeping sickness. On the other hand, traditional practitioners are located within the community area. By this, they are readily available and reachable local health providers. In this respect, it was estimated that the ratio of traditional practitioners to the population in Africa is 1:500, compared to 1:40′000 for medical doctors (Abdullahi, 2011). A new regional diagnostic project including the northern border zone of Angola (provinces of Zaire and Cabinda) is currently being tested and analyzed. It is based on passive screening aims at detecting cases in early phase by the combination of three new diagnostic tests, namely the rapid diagnostic test (RDT), the fluorescence microscopy LED (FM-LED), and loop-mediated isothermal amplification of DNA [LAMP] (Kuikumbi, 2018). These novel screening tests are implemented as routine tests in all health care units and any new patient should undergo this screening procedure. This new diagnostic strategy aims at detecting early phase cases and minimizing the distances by offering novel screening tests in all health care units. Reducing distance to treatment centers directly improves affordability of the treatment by reducing indirect costs like transport and food expenses.

A considerable amount of research has been conducted on health seeking behavior of patients suffering from chronic diseases like TB or HIV (Audet et al., 2012; Hatchett et al., 2004; Jørstad et al., 2018; Luis et al., 2011; Naidoo, 2014; Ngwira et al., 2018; SaMal, 2016; Santos et al., 2018; Sodi and Phethi, 2017). Few studies investigated health seeking behavior of patients with sleeping sickness (Hasker et al., 2011; Mpanya et al., 2012; Odiit et al., 2004). In a study run in Uganda among sleeping sickness patients, Odiit et al. mentioned that only one patient of 119 (0,8%) "admitted that he had first seen a traditional healer" (p.343) before visiting a medical health facility. A second study examined the health seeking behavior of 66 HAT-patients in the Democratic Republic of Congo and showed that 23 (34%) had first consulted a "unqualified private practitioner " (p.871), without further specification on the type of local care provider (Hasker et al., 2011). Our exploratory study points out for the first time an important frequency of use (40%) of folk medicine before medical treatment of HAT.

To get a deeper understanding of the causes that exert an impact on the health seeking behavior for sleeping sickness in Angola, detailed investigations on the patients' therapeutic itineraries have to be carried out. Aspects to be included are among others constraints and prohibition associated to reference treatment (Mpanya et al., 2015) or drug toxicity and costs (Robays et al., 2007). In the Democratic Republic of Congo, these were identified as significant factors which lead to a reduction of non- or low-adherence of local communities to medical prevention and treatment programs.

4.2. Ethnomedical use and antitrypanosomal activity of the studied plants

Of the 37 reported plants, 7 could not be identified because of lack of complete specimen.[3] This highlights the challenge of ethnopharmacological research. A botanical student of University of Agostinho Neto (Luanda) aided as a plant collector, and did several field walks in order to gather missing parts of specimen. Nevertheless, not all reported plants could be collected in a complete set, due for example to limited availability of respondents, time or financial constraints. Regarding conservation status, poor availability of data made it difficult to assess the potentially endangered species. Nevertheless, consultation of IUCN Red List (https://www.iucnredlist.org/) indicated *Fleroya stipulosa (DC.) Y.F. Deng* as being vulnerable and the book by (Costa et al., 2009) that covers this subject didn't point out any of the studied species as being threatened.

In view of the botanical species cited and the low number of known reported plants by the patients group (only 7 plants were mentioned), the distribution of knowledge of plants used to manage trypanosomiasis and its symptoms seems to be rather a specialized knowledge belonging to specialists group rather than to lay people. This aspect can be supported by the results obtained from the study of (Göhre et al., 2016), where out of 82 individuals surveyed in Uíge province of Angola and 30 different use-reports for different disorders mentioned, none referred to sleeping sickness. This shows that the knowledge of specific herbal remedies is rather in hand of a small circle of specialists, what is not surprising due to complex signs and issues of this parasitic disease. As can be seen from Table 2, a large part of the plants were mentioned only by a single informant, and few plants were cited twice or threefold. It highlights the complexity of the disease and could indicate that there is no plant that obviously responds to this sickness. It can also be explained by the explorative character of the study and the small sample size of the informants groups. Another reason for the weak interrelationship between used plants and specialists could be the secrecy of local knowledge and family heritage. However, one plant, namely *Crossopteryx febrifuga* has gathered the most votes (6 use-report) and was mentioned by both groups of informants. The plant is known for its febrifuge, antitussive, antidiarrheal and analgesic proprieties (Pousset, 2004). Among the different herbal preparations this plant was mentioned in this work to be applied as a juice arising from the crushed leaves into the eyes and the nose in order to "clean the eyes and reestablish a blurred vision" and "fight the sleepiness". The decoction of the roots was administered as a tonic drink enabling fighting the great tiredness that accompanies the disease. Interestingly, 2 studies reported a similar route of administration in Congo (Brazzaville). First (Maiga et al., 2006), mentioned that the "*liquid is administrated into the nose for headache and into the eyes for the conjunctivitis caused by filariae*". Another information arising from this source is that the leaves are "*taken as tonic, and they are put into some prescriptions for mental trouble*". Moreover, it is said that the plant is also used against epilepsy, which is related to convulsion, a symptom which can appear in the second stage of the disease. In the second study (Banzouzi et al., 2008), led a survey on analgesic and psychotropic plants in Congo (Brazzaville) and their findings confirmed the ethnomedicinal use of *C. febrifuga* for these

[3] The plant material will be used for future molecular identification.

Table 5
Main representative references of the reported plants and their antitrypanosomal activity.

STUDIED PLANTS	REPORTED IN VITRO ANTITRYPANOSOMAL ACTIVITY			REPORTED IN VIVO ANTITRYPANOSOMAL ACTIVITY			REPORTED IDENTIFIED ACTIVE COMPOUND				REFERENCES
Scientific name[part used]	Type of extract [plant part]/country	parasite	IC_{50} or MIC [µg/ml]	Type of extract[plant part]/country	animal & parasite	activity	Type of extract [plant part]/country	parasite	cpd	IC_{50} or MIC [µg/ml]	
***Nymphaea lotus* L., ^{Wp}**				MeOH70%^{WP}/Nigeria	T.b.b & mice	3					Garba et al. (2015)
***Entada abyssinica A.Rich*^{R}**	Aq.^{R}/Uganda	T.b.r	≤56[a]								Freiburghaus et al. (1996b)
	MeOH^{R}_F/Uganda	T.b.r	3.3 ± 1.3								Freiburghaus et al. (1996b)
	PE^{R}_F/Uganda	T.b.r	≤0.4 ± 0.2								Freiburghaus et al. (1996b)
	DCM^{R}_F/Uganda	T.b.r	≤0.5 ± 0.3				DCM^{R}/Uganda	T.b.r	1	2.5 ± 0.2	(Freiburghaus et al., 1996b, 1998)
	EtOH^{B}/Ivory coast	T.b.r	9								Atindehou et al. (2004)
							DCM^{SB}/Cameroon	T.b.b	2	1.7 µM	Nyasse et al. (2004)
	MeOH^{SB}/Tanzania	T.b.b	46.39 (SI:3.24)								Nibret et al. (2010)
	DCM^{SB}/Tanzania	T.b.b	56.21 (SI:1.85)								Nibret et al. (2010)
				EtOH^{RT}/Tanzania	T.b.b & mice	2					Sempombe et al. (2014)
***Sarcocephalus latifolius (Sm.) E.A.Bruce*^{R}**				EtOH^{RT}	T.b.b & mice	2					Madubunyi (1996)
				Aq.^{R}	T.b.b & mice	1					Youan et al. (1997)
	MeOH^{R}/Nigeria	T.b.b	˃500								Camacho et al. (2003)
	MeOH^{RB}, DCM^{RB}/Mali	T.b.b	≤10[a]								Bizimana et al. (2006)
	Aq.^{SB}, MeOH^{SB}/Nigeria	T.c	NA								Maikai and Kobo (2008)
	Hex, EtoAc, MeOH^{B}/Nigeria	T.b.b	NA				EtoAc^{B}/Nigeria	T.b.b	3	12.5[a]	Igoli et al. (2011)
				Aq.^{L}/Nigeria	T.b.b & rats	1					Olanrewaju et al. (2014)
				Aq.^{SB}/Nigeria	T.b.b & rats	2					Longdet et al. (2014)
				MeOH^{SB}/Nigeria	T.b.c & rats	2					Yusuf et al. (2005)
***Crossopteryx febrifuga (Afzel.ex G.Don) Benth* ^{L,R}**	MeOH80%^{L},RDC	T.b.b	39 ± 3.3 (SI: > 1.6)	Aq.^{SB}/NA	T.b.c & rats	2					Mesia et al. (2008)
		T.cruzi	> 64								
****Carica papaya* ^{L,R}**				CHCl3^{S}/Mexico	T.cruzi & mice	2					Jiménez-Coello et al. (2013)
							MeOH–NH4OH^{L}/Indonesia	T.b.r T.cruzi	4	12.7 µM 16.3 µM	Julianti et al. (2014)
***Vitex madiensis Oliv.*^{L}**	MeOH^{L}/Nigeria	T.b.r	14.2								Nwodo et al. (2012)
							MeOH_VLC_DCM_F^{L}/Nigeria	T.b.r	5	4.7 (SI: 9.8)	Nwodo et al. (2015b)
***Momordica charantia* L.^{AeP}**	MeOH80%^{WP}/RDC	T.b.b	7 ± 1.3 (SI:0.4)								Mesia et al. (2008)
	EtOH95%^{L}/Brasil	T.cruzi	46.06								Santos et al. (2012)
	Fruit (Bitter lemon)	T.brucei	NA								Phillips et al. (2013)

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Table 5 (*continued*)

STUDIED PLANTS	REPORTED IN VITRO ANTITRYPANOSOMAL ACTIVITY			REPORTED IN VIVO ANTITRYPANOSOMAL ACTIVITY			REPORTED IDENTIFIED ACTIVE COMPOUND				REFERENCES
Scientific name[part used]	Type of extract [plant part]/country	parasite	IC_{50} or MIC [μg/ml]	Type of extract[plant part]/country	animal & parasite	activity	Type of extract [plant part]/country	parasite	cpd	IC_{50} or MIC [μg/ml]	
Securidaca longipedunculata Fresen. [R]	$MeOH^{RB}$ and $Aq.^{RB}$/Tanzania	T.b.r	56^{MIC}								Freiburghaus et al. (1996a)
	$MeOH^{R}$/Nigeria	T.b.b, T.cg	NA								Atawodi et al. (2003)
	$Aq.^{R}$, $MeOH^{R}$, DCM^{R}/Mali	T.b.b	not active								Bizimana et al. (2006)
	DCM^{R}/Mali and Brukina faso	T.b.b	50[a] (SI > 10)	DCM^{R}/Mali and Brukina faso	T.b.b & mice	2					Aderbauer et al. (2008)
	DCM^{NI}/Tanzania	T.b.b	11.20 (SI:12.03)								Nibret et al. (2010)
				$Aq.^{R}$/Nigeria	T.b & rats	2					Haruna et al. (2013a)
				$MeOH\_VLC\_EtOAc^{R}$/Nigeria	T.b.b & mice/rats	2					Haruna et al. (2013b)
				$Aq.^{R}$/Nigeria	T.b.b & rats	2					Abubakar et al. (2005)
	$MeOH^{R}$/Nigeria	T.b.b	5[a]	$MeOH^{R}$/Nigeria	T.b.b & rats	2					Gabriel et al. (2015)
	$MeOH^{SB}$, $EtoAc^{SB}$,$Aq.^{SB}$,/Nigeria	T.b.b	NA	$MeOH^{SB}$, $EtoAc^{SB}$, Aq^{SB},/Nigeria	T.b.b & rats	1					Tauheed et al. (2016)
				$MeOH^{SB}$, $EtoAc^{SB}$, Aq^{SB},/Nigeria	T.b.b & rats	2					Tauheed et al. (2017)
Cymbopogon densiflorus (Steud.)Stapf [Fr, Fl]	$MeOH80\%^{WP}$/Congo	T.b.b	33 ± 1.3								Mesia et al. (2008)
Smilax anceps Willd. [R]	$MeOH90\%^{RH}$/Ivory coast	T.b.r	> 25								Atindehou et al. (2004)
****Senna occidentalis (L.) Link*** [R]	$EtOH95\%^{L}$/Nigeria	T.b.b	NA	$EtOH95\%^{L}$/Nigeria	T.b.b & rats	2					Ibrahim et al. (2010)
				$EtOH95\%^{L}$/Nigeria	T.b.b & mice	2					Mustapha et al. (2013)
Monodora myristica (Gaertn.) Dunal [L]	DCM^{S}/Ivory coast	T.b.b	NA								Okpekon et al. (2004)
	$EtoAc\_F^{S}$/Nigeria	T.b.b	3.125[a]				$EtoAc\_F^{S}$/Nigeria	T.b.b	6 7	25[a] 12.5[a]	Igoli et al. (2011)
Ocimum gratissimum L. [L]	Aq (EO)[L]/Brazil	H. s.	91								Holetz et al. (2003)
	$MeOH80\%^{WP}$/RDC	T.b.b	32 ± 3.4 (SI:0.4)								Mesia et al. (2008)
		T. cruzi	26 ± 2.7 (SI:0.5)								
	$Aq.^{L}$/Nigeria	T.b.b	NA	$Aq.^{L}$/Nigeria	T.b.b & rats	2					Adamu et al. (2009)
				$Aq.^{L}$/Nigeria	T.b.b & rats	1					Olukunle et al. (2010)
	$EtoAc^{L}$/Nigeria	T.b.r	2.08 ± 0.01 (SI:29)								Abiodun et al. (2012)
	$Aq.^{L}$/RDC	T.b.b	7.58 (SI > 8.4)								Muganza et al. (2012)
		T. cruzi	30.52 (SI > 2.1)								
	Aq $(EO)^{Ni}$/Brazil	T. cruzi	11.5 (SI > 15.7)								Borges et al. (2012)
				70%$EtOH^{S}$/Nigeria	T.b.b & mice	2					Adelodun et al. (2013)
	$EtOH^{L}$/Benin	T.b.b	1.66 ± 0.48 (SI:12.89)								Kpoviessi et al. (2014)
	$EtOH^{S}$/Benin	T.b.b	1.29 ± 0.42 (SI:10.94)								
Xylopia aethiopica (Dunal)							$EtoAc\_F^{FR}$/Cameroon	T.b.b	8	27.04 ± 0.03 μM	Soh et al. (2013)

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Table 5 (*continued*)

STUDIED PLANTS	REPORTED IN VITRO ANTITRYPANOSOMAL ACTIVITY			REPORTED IN VIVO ANTITRYPANOSOMAL ACTIVITY			REPORTED IDENTIFIED ACTIVE COMPOUND				REFERENCES
Scientific name[part used]	Type of extract [plant part]/country	parasite	IC_{50} or MIC [µg/ml]	Type of extract[plant part]/country	animal & parasite	activity	Type of extract [plant part]/country	parasite	cpd	IC_{50} or MIC [µg/ml]	
***Chromolaena odorata (L.) R.M.King & h.Rob.*[L]**	$MeOH^{L}$/Malaysia	T.b.b	> 12 (SI:nd)								Norhayati et al. (2013)
***Bryophyllum pinnatum (Lam.) Oken.*[L]**	$Aq.^{L}$/Nigeria	T. evansi	NA								Alhaji et al. (2014)
		T. cg	NA								
	DCM^{L}, $MeOH^{L}$	T.b.r, T.cruzi	NA								Gachet et al. (2010)
***Azadirachta indica A.Juss.*[L]**				$MeOH\_FIII^{L}$/Nigeria	T.b.b & rats	3					NOK et al. (1993)
	$CHCl_3{}^{L}$/Venezuela	T. cruzi	NA								Yanes et al. (2004)
				DCM^{B}/Kenya	T.b.r & mice	2					Ngure et al. (2009)
				Aq.,DCM, $MeOH^{SB}$/Kenya	T.b.r & mice	1					Peter et al. (2009)
	$CHCl_3\_F^{L}$/Kenya	T.b.r	4.4 ± 0.0[a]				$CHCl_3\_F^{L}$/Kenya	T.b.r	9	6.9	Githua et al. (2010)
									10	15.6	
									11	7.8	
	$EtOH^{SB}$/Nigeria	T.b.b	NA	$EtOH^{SB}$/Nigeria	T.b.b & rats	3					Mbaya et al. (2010)
	$MeOH^{S}$/Nigeria	T. evansi	NA	$MeOH\_F3^{S}$/Nigeria	T.evansi & rats	2					Habila et al. (2011)
	$Aq.(EO)^{L}$/Cameroon	T.b.b	15.21 ± 0.97 (SI > 6.57)								Kamte et al. (2017)

Column title abbreviations: IC_{50}: half maximal inhibitory concentration; MIC: minimum inhibitory concentration; cpd: compound; Plant parts' abbreviations: R: root; B: bark; SB: stem bark; RT: root bark; L: leaves; WP: whole plant; Aep: aerial part; S: stem; RH: rhizome. Solvents' abbreviations: Aq: aqueous; MeOH: methanol; PE: petroleum ether; DCM: dichloromethane; EtOH: ethanol; Hex: hexane; EtoAC: ethylacetate; $CHCL_3$: chloroform; Aq.(EO): aqueous fraction of essential oil. Country abbreviation: RDC: Republic Democratic of Congo. Extracts' fractions abbreviations: MeOH_F: methanolic fraction; PE_F: petroleum ether fraction; DCM_F: dichloromethane fraction; MeOH_NH4OH_F: methanol ammonium hydroxide fraction; MeOH VLC_DCM_F: methanol vacuum liquid chromatography dichloromethane fraction E; MeOH_VLC_EtOAc: methanol vacuum liquid chromatography ethylacetate extract; EtoAc_F: ethylacetate fraction; $MeOH\_FIII^{L}$: methanol extract fraction III: MeOH_F3: methanol extract fraction 3. Parasites models' abbreviations: T.b.r: *Trypanosoma brucei rhodesiense*; T.b.b: *Trypanosoma brucei brucei*; T.cruzi: *Trypanosoma cruzi*; T.cg: *Trypanosoma congolense*; T. evansi: *Trypanosoma evansi*; H.s: *Herpetomonas samuelpessoai*. Compound number: 1: diasteroisomer of kolavenol; 2: monomethyl ester-15-kolavic acid; 3: naucleidinal alkaloid; 4: carpaine; 5: artemetin: 6: 1H-indol-5-yl)methanol; 7: 4-(1H-indol-5-yl)but-3-en-2-one; 8:15-oxo-ent-kaur-16-en-19-oic acid; 9-11: tetranotriterpenoid. Categorisation of *in vivo* activity: 1: no activity; 2: transitory decrease in parasitemia; 3: complete parasite clearance. NA means that the results were not expressed as IC_{50} values or MIC, thus are not available. The selectivity index (SI) was reported in the table, when it was given in the referenced literature.

[a] Reported MIC values.

effects, depicting even the fact that the leaves of *C. febrifuga* were specifically used for their psychotropic properties, contrary to the roots which were administered as an analgesic remedy. At the time of Belgian Congo, the maceration of the bark of *C. febrifuga* was reported to be used against trypanosomiasis (Staner and Boutique, 1937). In Mozambique, the roots are taken as a febrifuge (Maiga et al., 2006). In Angola, a recent large-scale ethnobotanical study conducted in northern province of Uíge (Lautenschläger et al., 2018) reported *C. febrifuga* to the use-category "madness". Out of these various ethnomedicinal practices from Angola and neighbouring countries, *C. febrifuga* is confirmed to be a medicinal plant which is taken as a tonic, pain reliever, febrifuge, against mental disorder or epilepsy. These particular symptoms are encountered in the course of sleeping sickness, thus using a medicinal plant known to treat such ailment makes sense. In the light of the above mentioned aspects, the ethnomedicinal use of *C. febrifuga* finds support in traditional practices and *in vitro* studies confirmed the analgesic and antipyretic activity of the plant (Salawu et al., 2008). Glycosides flavonoids have been isolated from the leaves of *C. febrifuga* (Tomás-Barberán and Hostettmann, 1988). A large study assessing flavonoids and their analogues for their antitrypanosomal activity (Tasdemir et al., 2006) suggests that *C. febrifuga* glycoside flavonoids could have a similar activity.

Momordica charantia, *Palisota schweinfurthii* and *Vitex madiensis* were each mentioned by three different informants. *M. charantia*, also known as bitter lemon, is famous for its effectiveness against diabetes (Kharb et al., 2019; Leung et al., 2009). Traditional preparations are commonly used for external applications in wounds healing and skin diseases and internally as a remedy to treat worms and menstrual problems (Ahmad et al., 2016; Beloin et al., 2005). In South Africa a decoction of the leaves is recommended to act on the blood and sugar level (Mokganya and Tshisikhawe, 2019), in Ivory Coast as an antimalarial as well as antidiabetic remedy (Konkon et al., 2017) and in Angola as a febrifuge (Göhre et al., 2016). Among the various medicinal practices, the plant was never reported in the management of sleeping sickness. The same occurs for *Palisota schweinfurthii,* for which no reports against trypanosomiasis could be found. In folk medicine, *Vitex madiensis* has been reported to fight malaria in Gabon (Ondo et al., 2012) and Mali (Diarra et al., 2015) and schistosomiasis in Burkina Faso (Nacoulma-Ouédraogo, 1996). In Nigeria, Nwodo et al. mentioned its use against sleeping sickness without clearly describing the mode of preparation and usage (Nwodo et al., 2015b). A related species, *Vitex ferruginea* was described in a traditional preparation against sleeping sickness(Sifuma, 2011) and the maceration of the leaves is used as a head bath in case of psychosomatic troubles in Congo (Kinshasa) (Mbuta et al., 2012). In our work, *Vitex madiensis* was reported to be used directly, by applying ocular drops arising from the squeezed leaves mixed with local alcoholic beverage called "maruvo" and made of palm wine. Interestingly, *in vitro* investigations confirmed the presence of bioactive flavonoids in the alcoholic extract of the leaves, thus providing preliminary evidence of the antitrypanosomal potential of this traditional preparation. (Nwodo et al., 2013; Nwodo. et al., 2015b). From the foregoing, the recourse to *Crossopteryx febrifuga* and *Vitex madiensis* in the management of sleeping sickness and its symptoms could be correlated to a medicinal practice in use. On the contrary, the use of *Palisota schweinfurthii* and *Momordica charantia* couldn't be corroborate by ethnomedicinal data.

Looking further at the cited plants in Table 2, seven species have seen their medicinal usage against sleeping sickness being supported by ethnobotanical surveys, namely *Azadirachta indica*, *Senna occidentalis*, *Securidaca longipedunculata*, *Entada abyssinica*, *Sarcocephalus latifolius*, *Brillantaisia owariensis* and *Nicotiana tabacum*. The leaves of the latter in association with *Boswellia dalzielli* and *Adenium obesum* were given to fight "nagana" (animal trypanosomiasis) in Nigeria's Kaduna state (Atawodi et al., 2002) and alone in southern Ethiopia (Shilema et al., 2013). In our work, the juice of the fresh crushed leaves of *N. tabacum* was prescribed as nasal and eye drops by one of the inquired specialist, claiming it "awakes" the sufferer" and "alleviates headaches". Similar herbal prescription was found in Congo (Brazzavile) where the leaves juice of *N. tabacum* is mixed to the one of *Solanum lycopersicum* to fight trypanosomiasis (Adjanohoun and Sita, 1988). In addition, the leaves of *N. tabacum* are recommended for two HAT-related symptoms, namely strong headache (migraine) and epilepsy, in traditional practice in Equateur province of the Republic Democratic of Congo (Mbuta et al., 2012). However, *N. tabacum* has never been investigated for its antitrypanosomal activity. *Sarcocephalus latifolius*, commonly called African peach, is a typical savannah tree, largely used throughout tropical regions for diverse medicinal purposes. Besides its well-known usage against malaria and fever, in Angola the roots are found in local markets of Uíge province and sold as tonic (Lautenschläger et al., 2018). Concerning trypanosomiasis, one old work revealed the use of this plant against the disease in Ivory Coast (Bouquet and Debray, 1974) and its roots bark was mentioned in Mali to treat this affection (Bizimana et al., 2006). *Brillantaisia owariensis* is described in a polyherbal preparation made of 2 other plants as a remedy to fight trypanosomiasis in Equateur province of the neighbor country Congo (Kinshasa) (Mbuta et al., 2012). In Angola, the plant is mentioned in the large-scale ethnobotanical survey led in province of Uíge (Lautenschläger et al., 2018), mainly to fight heart problem, blood pressure and it is several times cited against headache and also against epilepsy and madness. These findings corroborate ours, where *B. owariensis* was prescribed to treat the suffering of headache, madness and convulsions, all symptoms induced by this disease. *Entada abyssinica*'s medicinal use in local herbal preparation has been reported twice from the southern region of Uganda. In both studies, the roots are prescribed, either after infusion or decoction, as an oral administration to fight trypanosomiasis (Freiburghaus et al., 1996b; Hamill et al., 2003). In Angola, usage of *E. abyssinica* in the management of sleeping sickness was not strictly confirmed by another study. However, the roots were cited to be used against two HAT-related symptoms, that are epilepsy and headache (Lautenschläger et al., 2018). *Securidaca longipedunculata, Senna occidentalis* and *Azadirachta indica*, three important multipurpose plants in African traditional medicine, have been mentioned in herbal remedies against human or animal sleeping sickness in Senegal (Kerharo and Adam, 1964), Congo Brazzaville (Diafouka, 1997) and in Nigeria (Maikai et al., 2010) respectively. Moreover, the roots of *S. longipedunculata* are generally used against headache, fever and convulsion, all HAT-related symptoms (Mongalo et al., 2015).

Interestingly *B. owariensis*, *Vitex madiensis and Securidaca longipedunculata* seem to be used in the cure of mental suffering arising from supernatural or evil cause (Moukouta and Pewzner-Apeloig, 2002; Sobiecki, 2008). In this context, their use echoes mental or behavioral disorders occurring in the second phase of the disease and underlines its association with supernatural or magical forces. Of 30 plants mentioned in our study, our ethnobotanical literature search provided support for the ethnomedical claim for 8 species with a reliable concordance of the plant part used. Other plants like *Ocimum gratissimum* or *Nymphaea lotus*, haven't been cited in ethnobotanical studies against trypanosomiasis per se, however their usage covers several HAT-related symptoms like strong headache, fever, convulsion or mental disorders. Therefore, about one third of the reported plants in this work could be correlated with the ethnomedicinal practice against sleeping sickness and its symptoms.

The antitrypanosomal potential of African medicinal plants and natural compounds has been reviewed in the last decade by (Ibrahim et al., 2014), (Simoben et al., 2018), (Ioset, 2008) and (Nwodo et al., 2015). Starting from there, a literature review of the studied plants revealed that out of the 30 identified species, 17 (56%) had their antitrypanosomal activity supported by *in vitro* and/or *in vivo* studies (see Table 5) namely *Nymphaea lotus, Entada abyssinica, Sarcocephalus latifolius, Crossopteryx febrifuga, Carica papaya, Vitex madiensis, Momordica charantia, Securidaca longipedunculata, Cymbopogon densiflorus, Smilax anceps, Senna occidentalis, Monodora myristica, Ocimum gratissimum,*

Xylopia aethiopica, Chromolaena odorata, Bryophyllum pinnatum, Azadirachta indica. Of this panel of 17 plants, *C. febrifuga* is the only one that was mentioned by specialists and patients, whereas *O. gratissimum*, *X. aethiopica*, *C. odorata* and *M. myristica* are the 4 species reported by the patients only. The 12 remaining plants were mentioned specifically by the involved specialists. The pharmacological results of the more promising plants of this work are discussed in the next paragraph according to the type of extract and plant part used. We have to consider that the traditional remedies of the studied plants were mainly prepared as a decoction, infusion or maceration, all water-dependent preparations. Therefore, a special focus will be given on aqueous extracts as the most reproducible traditional type of extract, while assessing the antitrypanosomal activity in the selected references.

The plant candidate that matches best between preclinical results and the traditional preparation mentioned in this work, is *Ocimum gratissimum* a medicinal plant mentioned only by patients and reported for its antitrypanosomal activity in 10 studies (see Table 5) This tropical aromatic plant, commonly named African basil, is widely spread and easily accessible in Angola for the local population who uses it either as condiment or remedy against diarrhea, stomach disorders, urinary infections, headaches, coughs and bronchitis (Da Costa and Pedro, 2013). The essential oil of *O. gratissimum* has demonstrated antibacterial and antifungal activity and its major compound eugenol showed promising antiprotozoal activity when assayed against the amastigote and promastigote forms of *Leishmania amazonensis* (Ueda-Nakamura et al., 2006). In our work, the traditional preparation of *O. gratissimum* was made of fresh leaves or boiled in decoction. Two *in vitro* studies (Adamu et al., 2009; Muganza et al., 2012) and two *in vivo* assays (Adamu et al., 2009; Olukunle et al., 2010) tested the aqueous extract of the leaves of *O. gratissimum against Trypanosoma brucei* spp.. The *in vitro* results were variable with one study demonstrated an inhibitory activity (IC_{50} = 7.58 μg/ml against *T.b.brucei*) as to the *in vivo* results, which at best reported prolonged time of survival of the infected animal. The most interesting *in vitro* outcome was obtained with the ethanol extract of the leaves assayed against *T.b.brucei* which exhibited an IC_{50} value of 1.66 μg/ml without being cytotoxic (SI: 12.89) (Kpoviessi et al., 2014). From the foregoing, the use of the leaves of *O. gratissimum* prepared traditionally as a decoction to fight sleeping sickness is supported by these pre-clinical data.

A second plant, intensively investigated and which counts in all 8 studies assessing its antitrypanosomal potential is *Azadirachta indica.* The neem or Margosa tree, a tropical evergreen plant, is known since ages in the Indian systems of medicines and considered as the “wonder tree” being an invaluable source for a variety of medicinal properties (Khetarpal, 2010; Saleem et al., 2018; Zeenat et al., 2018). In folk medicine the neem drug is used for various ailments such as inflammatory and febrile disease, cutaneous affections, measles, smallpox, earache, stomachache and burning sensations. The antimalarial use of the leaves and stem bark has been reviewed (Sofowora, 1996; Subapriya and Nagini, 2005), some studies reporting antimalarial effect (MacKinnon et al., 1997; Priyanka et al., 2013; Tepongning et al., 2018) and others being less clear (Rochanakij et al., 1985). Even though folk medicine doesn't mention *Azadirachta indica* against human sleeping sickness, nevertheless pharmacological investigations demonstrated that the alcoholic extracts of the leaves and stem bark of this plant obtained most promising *in vivo* outcomes with a complete parasitemia clearance in the infected animal after more than 30 days post infection (Mbaya et al., 2010; NOK et al., 1993). In our work, the use of leaves of *A. indica* was made as a prevention remedy. Thus, a traditional practitioner reported its repellent action by rubbing fresh leaves on the flies-exposed parts of the body. Different studies confirm its use as a natural fumigant to repel mosquitoes (Kweka et al., 2008; Seyoum et al., 2002) or as an herbal preparation made of leaves applied directly on the skin to treat various skin disorders like scabies, urticaria, eczema or skin infections (Zeenat et al., 2018). Neem oil made out of seed kernels extract was tested on rabbits' skin against *Aedes aegypti* mosquitoes and proved some repellent action without providing complete protection (Kiplang'at and Mwangi, 2013). A field study in Ethiopia on human volunteers confirmed the repellent efficacy of neem oil during 3 h against *Anopheles arabiensis* (Abiy et al., 2015). However, a direct application on the skin of the juice of the crushed leaves was never reported to date as a natural repellent. Azadirachtin, a bioactive triterpenoid of *A. indica* found in the seeds, leaves and bark has been positively correlated with the insecticidal property of neem oil. The presence of azadirachtin in the leaves could be responsible for the repellent action of the reported preparation which is directly applied on the skin. From the foregoing, the use of the leaves as a repellent has a proven rational and the very encouraging results obtained with the methanol extract of the leaves together with the stem bark extract should be considered for further investigation in the search for a novel drug candidate against trypanosomiasis.

Another plant that gathered most promising *in vivo* results is *Nymphaea lotus*. This plant, also called water lily, is an aquatic plant with white flowers widely spread in tropical Africa. In our work, the plant was reported to have served as an herbal remedy to fight sleeping sickness during epidemic periods in Uíge province. Traditional herbal preparations made of *N. lotus* are mentioned in case of cancer (Kayode et al., 2008), or stomach ulcers or as narcotic and sedative (John-Africa et al., 2012). It is prescribed in combination with other plants species to treat “tazo” (malaria) in the eastern region of Madagascar (Randrianarivelojosia et al., 2003). To the best of our knowledge, the recourse to water lilly in the preparation of a local remedy against sleeping sickness could not be confirmed. Nevertheless (Garba et al., 2015), provided very promising antitrypanosomal *in vivo* results with a 70% methanol extract of *N. lotus* reducing parasitemia in infected mice with *T.b.brucei* at a dose of 100 mg/kg/day. The phytochemical profile of the methanol extract revealed the presence of saponins, tannins, cardiac glycosides, and phlobatannins without identifying a bioactive constituent. Due to its *in vivo* antitrypanosomal potency, additional pharmacological studies should explore the antiprotozoal potential of *N. lotus*.

Three more species were assessed for their antitrypanosomal activity by more than five preclinical studies for each, namely *Entada abyssinica*, *Sarcocephalus latifolius* and *Securidaca longipeduncunlata.* Among the different studies, few tested specifically the aqueous extract of the plant's part used in the traditional preparation and only the aqueous extract of the roots of *S. longipedunculata* exhibited two positive *in vivo* results against *T.brucei brucei* with a transitory reduction in parasitemia (Abubakar et al., 2005; Haruna et al., 2013a). Moreover, Abubakar et al. showed that the extract improved hematological parameters in the infected rats. However, the aqueous extract of the roots *S. longipeduncunlata* when assayed *in vitro* against the same parasite wasn't active (Bizimana et al., 2006) what suggests that inactive *in vitro* precursor constituents may be metabolized in active substances *in vivo*. Root decoction of *Entada abyssinica* was correlated with a moderate outcome among the pharmacological data (MIC ≤ 56 μg/ml), nevertheless the dichloromethane extract of the rootbark demonstrated very encouraging *in vitro* results with an IC_{50} ≤ 0,5 μg/ml and isolation of a bioactive compound named diastereoisomer of kolavenol (IC_{50} = 2,5 μg/ml) (Freiburghaus et al., 1996a, 1998). Concerning *S. latifolius*, the variable results of the antitrypanosomal activity of the root extracts request for further investigation to clarify the inhibitory potential of this plant against *Trypanosoma brucei* ssp.

As we have seen from its ethnomedicinal uses, *Crossopteryx febrifuga* has various medicinal proprieties, which resulted in a wide range of pharmacological studies. However, few have investigated its trypanocid potential. Considering the leaves’ part, only one study assessed the antitrypanosomal activity of the methanolic extract against *T.b.brucei* which resulted in a weak inhibitory activity (IC_{50} = 39 ± 3.3 μg/ml) (Mesia et al., 2008). The roots were not analyzed for now. As the curative proprieties of the leaves and roots are correlated with the relief

of several HAT-symptoms, it would be worth investigating this plant for its antitrypanosomal potency.

Other plants like *Vitex madiensis*, *Momordica charantia*, *Smilax anceps* and *Chromolaena odorata* have obtained positive *in vitro* results for their alcoholic extract of the indicated plant's part against *Trypanosoma brucei* ssp. Artemetin, a flavonoid, was even isolated from the methanol extract of the leaves of *V. madiensis* and exhibited an IC_{50} value of 4.7 µg/ml against *T.b.rohdesiense*. Nevertheless, the aqueous extracts of these 3 species were not assessed so far. Considering the polarity range of the methanol extracts, we cannot exclude that an aqueous extract of the same plant part would show an inhibitory activity. Therefore, the antitrypanosomal potential of the reported traditional preparation for each of these 3 species should be assessed.

Of the 17 referenced plants, 3 species, namely *Monodora myristica, Cymbopogon densiflorus* and *Carica papaya*, haven't seen their traditional usage confirmed either by ethnobotanical surveys or by comparison with preclinical data.

When assessing plant candidates issued from traditional preparation, it should be kept in mind that the herbal treatment prescribed by the traditional practitioners was made of one to three recipes which comprises one or more different plants. Thus, the potential synergistic effect due to the plant combination is at preclinical level almost never taken into account. Furthermore, results discrepancy for a same extract tested against the same parasite model can be explained by the differences in study protocol, in phytochemical profile of the plant material. Consequently, the outcome of such a comparative analysis among various studies, which are realized in different countries, must be considered with precaution.

Nevertheless, if we consider the specific plant part used and the type of extract tested few of the reported medicinal plants match to the described antitrypanosomal activity. Among the 17 referenced plants, only 3 species, namely *Entada abyssinica*, *Securidaca longipeduncunlata* and *Ocimum gratissium* showed *in vitro* or/and *in vivo* evidence to corroborate the antitrypanosomal potential of the reported traditional preparation. In term of prevention, the traditional use of *Azadirachta indica* as a repellent could also be associated with referenced literature. *Ocimum gratissimum* and *Nymphaea lotus* displayed very promising *in vivo* results for non-aqueous extracts type with a complete parasitemia clearance. *Vitex madiensis*, *Momordica charantia*, *Smilax anceps*, *Chromolaena odorata* and *Crossopteryx febrifuga* lack assessment of the aqueous extract of the recommended plant component and should be therefore complemented. *Palisota schweinfurthii* which was cited 3 times and for which no HAT-related information is available should be investigated further.

4.3. Potential undesired or toxic side effects

Herbal medicines lack of standardization, and very few prescribed remedies have been rigorously tested for their toxicity, especially for their long-term effect. For this reason, it is important to address the potential risk of use of the studied plants, and report it to the concerned population. Several plants mentioned in this work raise important questions about potential toxicities.

Among these, tobacco (*Nicotiana tabacum*) and *Thevetia peruviana* could easily lead to acute toxicity accidents in case of overdoses. Tobacco plant is rich in nicotine, a powerful neurotoxic water-soluble alkaloid that is present in the leaves. *Thevetia peruviana* contains cardiotoxic glycosides in all parts of the plant, particularly in the sap and seeds. This widespread ornamental plant has been linked with numerous fatal intoxications in the tropics (Eddleston et al., 2000). As the use of its fruits was mentioned by one of our specialist, awareness needs to be raised about the use of its herbal preparation. Even more concerning is the use of *Aristolochia gigantea*, since the whole genus Aristolochia has been identified as nephrotoxic and carcinogenic due to the presence of aristolochic acids and/or aristolactams in all parts of these plants (Michl et al., 2014). Adverse effects can occur several weeks or months after intake, and such delayed and cumulative effects remain generally unsuspected by the users. *Securidaca longipedunculata* is another plant that should be suspected of potential danger (Liwa and Jaka, 2016; Mongalo et al., 2015). The fact that an interviewed traditional practitioner recommended an aqueous extract of the roots of this medicinal plant without even mentioning precaution of use for pregnant women points out the necessity to analyze the risk associated with the use of herbal preparations and to discuss it with the target population. Based on ethnobotanical reports, even if strong toxicological evidence is lacking, attention should be paid to herbal remedies containing *Sansevieria* sp. and *Smilax* sp. because both contain haemolytic saponins and are components of hunting poisons (Neuwinger, 1996). Similarly, *Capsicum frutescens,* although widely consumed as a spice, is not devoid of danger since some wild ecotypes are so rich in capsaicin and other pungent compounds that severe burns can occur (Neuwinger, 1996). The above mentioned plants highlight the need for a true pharmacovigilance in the field of traditional remedies, as emphasized by the World Health Organization (WHO, 2004). We will organize a “feed-back session” with the concerned population (users and providers of FM) in order to share these concerns and look for alternatives.

5. Conclusion

The explorative ethnomedicinal study part shows evidence that three main factors – accessibility, cultural acceptability and affordability – account for the recourse to folk medicine in the management of g-HAT in the studied areas. The frequency of use of folk medicine for g-HAT is significant, 40% of the inquired patients resorted to folk medicine before receiving reference treatment. Recognizing local perspectives and practices of HAT management in Angola will be essential for a comprehensive understanding of dynamics in a local healthcare system.

In an ethnobotanical outlook, and though Angola faced several epidemic g-HAT periods, none of the traditional practitioners claimed to be a specialist in relation to sleeping sickness. More than half of the 30 identified botanical species have been previously reported for their antitrypanosomal activity, which supports the ethnopharmacological approach. The use of herbal remedies seems not to be concomitant with the medical treatment, which reduces the risk of drug interaction between herbal drug and reference treatment.

This study shows supportive evidence for the ethnomedicinal use of some plant species as herbal treatment in the management of sleeping sickness. At the same time, some of the used plants raise serious concerns about toxicity. This work is a contribution to a more evidence based use of herbal remedies and a first step towards the validation of herbal preparations used in the management of trypanosomiasis in Angola and their potential usefulness.

Author contributions

NV, PM, JT, JF and PvE conceived and designed the study. NV and MKK performed the questionnaires and survey. NV and PMN collected the plants. PMN and EdC identified and authenticated the plants. NV and PvE analyzed the data. NV wrote the manuscript and PM, JF, PvE revised it.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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