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Review

Antimalarial activity of medicinal plants from the democratic republic of Congo: A review

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ABSTRACT

Ethnopharmacological relevance: Malaria is the most prevalent parasitic disease and the foremost cause of morbidity and mortality in the Democratic Republic of Congo. For the management of this disease, a large Congolese population recourses to traditional medicinal plants. To date the efficacy and safety of many of these plants have been validated scientifically in rodent malaria models. In order to generate scientific evidence of traditional remedies used in the Democratic Republic of Congo for the management of malaria, and show the potential of Congolese plants as a major source of antimalarial drugs, this review highlights the antiplasmodial and toxicological properties of the Congolese antimalarial plants investigated during the period of 1999–2014. In doing so, a useful resource for further complementary investigations is presented. Furthermore, this review may pave the way for the research and development of several available and affordable antimalarial phytomedicines.
Materials and methods: In order to get information on the different studies, a Google Scholar and PubMed literature search was performed using keywords (malaria, Congolese, medicinal plants, antiplasmodial/antimalarial activity, and toxicity). Data from non-indexed journals, Master and Doctoral dissertations were also collected.
Results: Approximately 120 extracts and fractions obtained from Congolese medicinal plants showed pronounced or good antiplasmodial activity. A number of compounds with interesting antiplasmodial properties were also isolated and identified. Some of these compounds constituted new scaffolds for the synthesis of promising antimalarial drugs. Interestingly, most of these extracts and compounds possessed high selective activity against *Plasmodium* parasites compared to mammalian cells. The efficacy and safety of several plant-derived products was confirmed in mice, and a good correlation was observed between *in vitro* and *in vivo* antimalarial activity. The formulation of several plant-derived products also led to some clinical trials and license of three plant-derived drugs (Manalaria®, Nsansiphos®, and Quinine Pharmakina®).
Conclusion: The obtained results partly justify and support the use of various medicinal plants to treat malaria in folk medicine in the Democratic Republic of Congo. Antimalarial plants used in Congolese traditional medicine represent an important source for the discovery and development of new antimalarial agents. However, in order to ensure the integration of a larger number of plant-derived products in the Congolese healthcare system, some parameters and trends should be considered in further researches, in agreement with the objectives of the "Traditional Medicine Strategy" proposed by the World Health Organization in 2013. These include evaluation of geographical and seasonal variation, investigation of reproductive biology, assessment of prophylactic antimalarial activity, evaluation of natural products as adjuvant antioxidant therapy for malaria, development of plant-based combination therapies and monitoring of herbal medicines in pharmacovigilance systems.

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Contents

1. Introduction

Malaria still remains one of the most devastating parasitic diseases in the world. In the Democratic Republic of Congo, it affects annually 12 million patients and causes nearly 100,000 deaths (PNLP, 2011; WHO, 2013a). The Democratic Republic of Congo (DR Congo) accounts for up to 15% of the estimated global malaria deaths. The vast majority of deaths occur in young children (6 months to 5 years of age) (WHO, 2013a). This malaria incidence is due to the high prevalence of *Plasmodium falciparum* (> 90% as monoinfection), the most dangerous of the human malaria parasites (Messina et al., 2011; Taylor et al., 2011, WHO, 2013a). The wide presence of *Anopheles gambiae*, the long-lived and human blood-feeding vector as well as environmental conditions for prolific breeding also contribute to the increased rates of malaria infection in the DR Congo (PNLP, 2011).

The objective of treating uncomplicated malaria is to cure the infection as rapidly as possible (WHO, 2010) thereby preventing progression to the severe forms of the disease. Malaria chemotherapy is an area with a continuous growth and revision due to the limited number of drugs currently available and the continuous development of resistance developed by the parasite to some of these drugs (e.g. chloroquine, sulfadoxine-pyrimethamine, mefloquine, halofantrine, etc.) (Carballeira, 2008). Moreover, lumefantrine, piperaquine, primaquine, proguanil and atovaquone could not fit the bill due to a variety of reasons which include side effects, pharmacokinetic mismatch and cost considerations. Despite its cardiotoxicity and hyperinsulinemic hypoglycemia induction, quinine, the first plant-derived antimalarial drug, remains a treatment of choice in severe falciparum malaria (WHO, 2010; PNLP, 2011).

Recent studies have shown that artemisinin, a sesquiterpene lactone extracted from *Artemisia annua*, is a rapid and potent antimalarial, killing chloroquine-resistant parasites. Artemisinin derivatives are currently the most important compounds in the therapeutic arsenal against malaria. Since 2001, the artemisinin-based combination therapies have been accepted by the Congolese government as the first-line treatment for *falciparum* malaria as recommended by the World Health Organization guidelines (WHO, 2010). These combination therapies add a new dimension to malaria therapy due to their potential to eliminate all asexual stages of *Plasmodium* spp. and to kill immature and developing gametocytes. However, reports on increased treatment failure and possible resistance development to these combinations are already available in different countries including the DR Congo (PNLP, 2005; Raman et al., 2011; Patel et al., 2014).

Therefore, there is an urgent need to discover new drugs (and pharmacophores) as potential replacements for quinine and artemisinin derivatives. However, a huge investment in the development of new (semi)synthetic antimalarial drugs is considered by the pharmaceutical industries as a risky affair because the populations from developing countries cannot afford to pay a high price for these drugs (Wink, 2012). Hence, the identification of antimalarial effects of classes of drug molecules that have already been evaluated as drug leads for other diseases represents a prospective, attractive and inexpensive strategy (Gelband and Seiter, 2007; Borhade et al., 2012; Pink et al., 2005).This approach known as the "piggyback approach" has been successfully applied to several plant-derived products such as curcumin (Memvanga et al., 2013a; Memvanga, 2013b).

Another more economical alternative to the development of synthetic drugs is the search for antimalarial plant extracts or secondary metabolites derived from them (Newman and Cragg, 2007; Wink, 2012). Indeed, ethnopharmacology is a very interesting resource in which new drugs and pharmacophores may be discovered. In this context, the DR Congo has a variety of plants associated with a diversity of traditional medicinal practices varying from one ethnic group to another (Kambu, 1990). However, despite the well-documented ethnobotanical and ethnopharmacological literature on Congolese antimalarial plants (Mabika, 1983; Bakana, 1984; Kambu, 1990; Pauwels, 1993; Biruniya, 1993; Defour, 1996; Kasuku et al., 1999; Mato, 2005; Musuyu Muganza, 2006; Fruth et al., 2011; Kasali et al., 2014), it is only recently that scientific validation concerning antiplasmodial activity, toxicity, phytochemistry, etc. of these plants used in traditional medicine has emerged.

In this review, we have attempted to take a look at the different researches undertaken on *in vitro* and *in vivo* antimalarial evaluation of Congolese antimalarial plants during the period of 1999–2014. The data obtained from bioguided fractionation, isolation and structure elucidation performed on these antimalarial plants are also highlighted. We thereby generate scientific evidence of traditional remedies used in the DR Congo for the management of malaria, and show the potential of Congolese plants as a major source of antimalarial drugs. In doing so, this review may pave the way for further complementary research as well as development of several available and affordable antimalarial phytomedicines, in line with the objectives of the "Traditional Medicine Strategy" proposed by the WHO (2013b).

2. *In vitro* antiplasmodial activity and cytotoxicity of plant-derived products

To identify Congolese plants with potential antiplasmodial activity, the majority of pharmacological studies focused on crude extracts and fractions. Some of these studies were also dedicated to callus cultures and isolated compounds. All the *in vitro* antiplasmodial testing was based on the parasite lactate dehydrogenase activity (Makler et al., 1993), the titrated [^{3}H]-hypoxanthine incorporation

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method (Desjardins et al., 1979) or a modified Rieckman schizont maturation method (Tona et al., 1999; Rieckmann et al., 1978). The antiplasmodial activity was assessed either on *P. falciparum* clinical isolates or *P. falciparum* laboratory strains. Among the laboratory strains, these were the chloroquine-sensitive (3D7, D6, NF54/64, Ghana, FCA 20, etc.), chloroquine-resistant (FcB1 and FcM29) and chloroquine-multidrug resistant (W2 and K1) strains.

According to the guidelines of World Health Organization and basic criteria for antiplasmodial drug discovery (Pink et al., 2005; Rasoanaivo et al., 2004), activities of extracts were classified as follow: high or pronounced activity ($IC_{50} \leq 5$ μg/ml); good or promising activity (5 μg/ml $< IC_{50} \leq 15$ μg/ml); moderate activity (15 μg/ml $< IC_{50} \leq 50$ μg/ml) and weak activity (50 μg/ml $< IC_{50} < 100$ μg/ml). A pure compound is defined as highly active when its $IC_{50} \leq 1$ μg/ml. Additionally, based on the ability to inhibit the growth of *P. falciparum* clinical isolates, extracts or fractions that inhibit 50% of schizonts maturation at concentrations lower than 5 μg/ml were considered as interesting samples.

2.1. *In vitro* antiplasmodial activity of crude extracts, fractions and calli

During the different antiplasmodial investigations, fresh or dried plant parts were used to obtain crude extracts, fractions or calli. The studied extracts and fractions were from up to 100 species belonging to 45 families (see Tables 1 and 2). It is important to note that unpublished results of a number of plant species have not been included in this review, due to their inappropriate study design.

The investigated medicinal plant species were collected from different provinces of the DR Congo, mainly in Kinshasa, Bandundu, Bas-Congo and Kasaï-Oriental during ethnobotanical or ethnopharmacological studies conducted among various traditional healers. In most of the cases, these plant species were identified at the Institut National d'Etudes et de Recherche en Agronomie (INERA, University of Kinshasa) where vouchers specimens were deposited.

Aqueous extracts were obtained by maceration or decoction in distilled water. The supernatants were then cooled, filtered and dried *in vacuo* or by lyophilization. On the other hand, organic extracts (80% methanol, 80% ethanol, dichloromethane, petroleum ether, etc.) were macerated, percolated or submitted to soxhlet extraction. The extractive solvents were then cooled, filtered and evaporated to dryness under reduced pressure at 40 °C using a rotary evaporator. In addition, some extracts were fractionated based on the Mitscher procedure (Mitcher et al., 1978) or the classical method described by Harborne (1998) using solvents of different polarities.

In this section, the antiplasmodial screening studies from Congolese plants are summarized. A summary of (highly) active and inactive extracts, fractions and isolated compounds is also given in Tables 1 and 2. The antiplasmodial activity of some of these plant-derived products was close to that found in samples from West, East and South Africa (Soh and Benoit-Vical, 2007; Gessler et al., 1994; Pillay et al., 2008).

In a first antiplasmodial evaluation on Congolese plants, Tona et al. (1999) investigated the antiplasmodial activity of the ethanolic and dichloromethane extracts from different parts of 9 Congolese medicinal plants used in Kinshasa. All the extracts and fractions were tested against isolated directly obtained from the blood of Congolese patients with acquired *P. falciparum* infection. Of these plant species, 7 extracts show more than 80% inhibition of *P. falciparum* growth at a concentration of 6 μg/ml. These were 4 dichloromethane extracts (from *Cassia occidentalis* leaves, *Euphorbia hirta* whole plant, *Garcinia kola* stem bark and *Phyllantus nuriri* whole plant), and 3 ethanolic extracts (from *E. hirta* whole plant, *G. kola* stem bark and *Cryptolepis sanguinolenta* root bark). The ethanolic and dichloromethane extracts from *Morinda lucida* leaves and *G. kola* seeds produced about 60% inhibition of *P. falciparum*. The ethanolic extract of *C. occidentalis* and of *P. niruri* as well as the dichloromethane extract of *C. sanguinolenta* also showed more than 60% inhibition of parasitaemia at the same concentration.

In the continuity of their antiplasmodial screening, Tona et al. (2004) investigated the *in vitro* antiplasmodial activity of ethanolic extracts and fractions from 7 antimalarial plants used in the DR Congo. Ethanolic extracts from *C. occidentalis* leaves, *E. hirta* whole plant, *G. kola* stem bark and *P. niruri* whole plant were the most active against *P. falciparum* clinical isolates ($IC_{50} < 3$ μg/ml) while those from *Vernonia amygdalina* leaves and *Tetracera poggei* leaves were less active ($10 < IC_{50} < 50$ μg/ml). The ethanolic extract from the leaves of *Morinda morindoides* has been shown to be inactive ($IC_{50} > 100$ μg/ml). However, the respective petroleum ether soluble fractions of these 7 ethanolic extracts exhibited a pronounced antiplasmodial activity ($IC_{50} < 3$ μg/ml). In addition, the isoamyl alcohol fractions from *E. hirta*, *V. amygdalina* and *P. niruri* showed IC_{50} values lower than 3 μg/ml. In another study, the methanolic extract of *V. amygdalina* leaves exhibited an antiplasmodial activity with IC_{50} value of 3.58 μg/ml against the *P. falciparum* FcM29-Cameroon strain (Ngbolua et al., 2011a).

Afterwards, Soh et al. (2009) evaluated the antiplasmodial activity of *P. niruri* leaves, stem bark and root bark collected from three different areas in the DR Congo, namely Lemba (in the neighborhood of University of Kinshasa), Kimwenza (located at 5 km of the University of Kinshasa) and Kisantu (located at 120 km of the University of Kinshasa). The authors demonstrated that whatever the cultivation area, both aqueous and ethanolic extracts of *P. niruri* leaves were (moderately) active *in vitro* against *P. falciparum* FcM29-Cameroon (chloroquine-resistant) with IC_{50} of 14–19 μg/ml and 19–25 μg/ml, respectively. By contrast, only the ethanolic extracts of *P. niruri* stem bark from Kimwenza were effective against this FcM29 strain ($IC_{50}=22$ μg/ml). In addition, all the extracts from *P. niruri* root bark, whatever the source area or the extraction solvents, exhibited $IC_{50} > 50$ μg/ml against the same strain of *P. falciparum*. These results might be supported by the fact that the metabolic profiles of *P. niruri* change with its geographical distribution (Kikakedimau et al., 2012). In order to amplify the production of secondary metabolites having antiplasmodial activity, the effects of gamma irradiation on seeds germination and plantlets growth of *P. odontadenius* were evaluated (Kikakedimau et al., 2014). The material irradiated with doses of gamma irradiation higher than 150 Gy showed better antiplasmodial activity than the non-irradiated material.

Referring to their traditional usage in the province of Kivu, Ndaya Tshibangu et al. (2002) evaluated the ability of 7 plants to inhibit the *in vitro* growth of *P. falciparum* (chloroquine-sensitive D6 strain and chloroquine-resistant W2 strain). Results of biological testing towards the D6 strain of *P. falciparum* indicated that 7 plant extracts exhibited antiplasmodial activity with $IC_{50} < 10$ μg/ml. These were the extracts of *Celosia trigyna* herbal plant (dichloromethane), *Cissampelos mucronata* root (ethyl acetate and methanolic), *M. arboreus* (dichloromethane and methanolic), *Otiophora pauciflora* herbal part (dichloromethane) and *Polyscias fulva* bark (dichloromethane). Additionally, a significant activity towards the chloroquine-resistant W2 strain was observed with the methanolic and ethyl acetate extract of *C. mucronata* ($IC_{50}=1.1–1.8$ μg/ml) as well as the dichloromethane extract of *M. arboreus* ($IC_{50}=7.7$ μg/ml).

In an *in vitro* antiplasmodial evaluation of medicinal plants from Sankuru district, Kasai-Oriental province, the activity of crude extracts and fractions from the partition of 80% methanolic extracts of *Croton mubango* stem bark, *Nauclea pobeguinii* stem

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bark and *Pyrenacantha staudtii* leaves were evaluated against a Congolese chloroquine-sensitive strain of *P. falciparum* (Mesia et al., 2005). The methanolic and dichloromethane extracts of *C. mubango*, and the dichloromethane extracts of *N. pobeguinii* and *P. staudtii* were the most active ($IC_{50} < 1$ μg/ml). The antiplasmodial activity obtained with aqueous extracts was ranged as follow: *C. mubango* ($IC_{50} = 3.2$ μg/ml), *N. pobeguinii* ($IC_{50} = 5.3$ μg/ml) and *P. staudtii* ($IC_{50} = 15.2$ μg/ml). The 80% methanolic extracts of *C. mubango* and *N. pobeguinii* exhibited high antiplasmodial activity with $IC_{50} < 5$ μg/ml while that of *P. staudtii* was inactive ($IC_{50} > 100$ μg/ml).

In continuation of the aforementioned study, aqueous and 80% ethanolic extracts of stem bark of *N. pobeguinii* were evaluated for their *in vitro* activity against the chloroquine-sensitive Ghanaian strain of *P. falciparum* (Mesia et al., 2010a). These extracts displayed moderate *in vitro* antiplasmodial activity with IC_{50} ranging from 32 μg/ml to 44 μg/ml. The results partly support and justify the use of this plant in combination with *C. occidentalis* in Congolese traditional medicine for the treatment of uncomplicated malaria.

In another study, 45 ethnobotanically described antiprotozoal plants, collected from Sankuru district, Kasai-Oriental province were screened (Mesia et al., 2008). These plants were tested against *P. falciparum* (chloroquine-sensitive) Ghana strain. Based on this investigation, only the 80% methanol extract from 6 plants exhibited pronounced or good antiplasmodial activity. Among them, extracts from *Microdesmis puberula* leaves, *Lantana camara* leaves and *Ocimum gratissimum* whole plant displayed good activity (5 μg/ml < IC_{50} < 15 μg/ml). The most active extracts were those from *Alchornea cordifolia* leaves, *Sapium cornutum* stem bark, *Polyathia suaveolens* stem bark and *Triclisia gilletii* stem bark ($IC_{50} < 5$ μg/ml) (see Table 1).

Furthermore, a recent follow-up study on *T. gilletii* was performed (Kikueta et al., 2013). The aqueous, 80% methanol and total alkaloid extracts, and a series of fractions and subfractions from the leaves, stem and root bark of *T. gilletii* were assayed for their antiplasmodial activity. Many samples from the three plant parts exhibited pronounced activity against a Congolese chloroquine-sensitive strain of *P. falciparum* with some IC_{50} values lower than 0.02 μg/ml, and against the K1 strain, with some IC_{50} lower than 0.25 μg/ml (see Table 1).

Similarly, the aqueous, 80% methanol and total alkaloid extracts, and a series of fractions and subfractions from the leaves, stem and root bark of *Alstonia congensis* were tested *in vitro* for their antiplasmodial activity against the chloroquine-pyrimethamine-resistant K1 strain of *P. falciparum* (Lumpu et al., 2013). Interestingly, all the extracts and most fractions exhibited pronounced or good antiplasmodial activity. Nevertheless, the authors noted that the different aqueous extracts, which constitute the typical traditional remedy, displayed lower IC_{50} values than the total methanol 80% extracts (see Table 1).

Since *Epinetrum villosum* is used traditionally to treat fever and malaria in the Lomela area, Kasaï-Oriental province, a pharmacognostic study was conducted to confirm its antiplasmodial activity (Longanga Otshudi et al., 2005). The results indicated that the aqueous extract of the root bark of *E. villosum* displayed a potent effect against *P. falciparum* FcB1-Colombia (chloroquine-resistant strain) with an IC_{50} of 0.20 μg/ml.

Different extracts from the leaves of *M. morindoides* were also tested for their potential *in vitro* antiplasmodial activity (Cimanga et al., 2009). However, the ethanol and dichloromethane extracts were inactive against a Congolese chloroquine-sensitive strain of *P. falciparum* ($IC_{50} > 100$ μg/ml), as reported previously (Tona et al., 2004). By contrast, the petroleum ether, isoamylic alcohol and chloroform soluble fractions from the partition of ethanol extract showed high or promising antiplasmodial activity with IC_{50} values of 1.8, 15.3 and 8.8 μg/ml against the same strain, respectively. Additionally, the chloroform soluble fraction from the partition of the 80% methanol exhibited good antiplasmodial activity with IC_{50} value of 8.3 μg/ml against the chloroquine-sensitive NF54/64 strain of *P. falciparum* (Cimanga et al., 2009).

Lusakibanza et al. (2010) bioassayed against the *P. falciparum* 3D7 and W2 strains the methanolic and dichloromethane extracts of 5 plants that are frequently used as antimalarial remedies in several provinces of the DR Congo. Among the 5 plants investigated, *Physalis angulata* whole plant and *Strychnos icaja* root bark showed a pronounced antiplasmodial activity against the two tested strains of *P. falciparum* ($IC_{50} < 3$ μg/ml) whereas *Anisopappus chinensis* whole plant displayed a good activity with an $IC_{50} < 15$ μg/ml. By contrast, the extracts of *Entandrophragma palustre* stem bark and *Melia azedarach* leaves showed a moderate antiplasmodial activity. In line with this study, Mangwala Kimpende et al. (2013) also evaluated the antiplasmodial activity of the aqueous extract of *P. angulata* and obtained an IC_{50} value of 11.36 μg/ml against the 3D7 strain.

The *in vitro* antiplasmodial evaluation of *E. palustre* stem bark, *Catharanthus roseus* leaves and *C. occidentalis* leaves as well as their ecological taxonomic equivalence growing in Madagascar was reported (Ngbolua et al., 2011b). The authors showed that, among the ecotypes from the DR Congo, only the ethanolic extracts of *C. occidentalis* were moderately active *in vitro* against the *P. falciparum* FcM29 strain ($IC_{50} = 16$ μg/ml).

Relying on an ethnopharmacological inventory conducted in the Bolongo area, Bandundu province, the antiplasmodial potential of 33 selected medicinal plants was evaluated (Muganza et al., 2012). To mimic the traditional methods of preparation, lyophilized aqueous extracts were used during this screening assay. Out of all the extracts tested, 9 aqueous decoctions were found to have pronounced or good activity against the chloroquine and pyrimethamine-resistant K1 strain of *P. falciparum*. Among them, the aqueous extracts from *Quassia africana* root bark and stem bark were the most active ones ($IC_{50} < 1.5$ μg/ml). The 7 other extracts (5 μg/ml < IC_{50} < 15 μg/ml) included *A. cordifolia* leaves, *Enantia chlorantha* stem bark, *Harungana madagascariensis* stem bark, *Isolana hexaloba* root bark, *O. gratissimum* leaves, *Piptadeniastrum africanum* stem bark, *Psidium guajava* leaves and *Triclisia dictyophilla* leaves.

The *in vitro* evaluation of the biological activity of different extracts, fractions and subfractions from *Brucea sumatrana* seeds indicated that aqueous, 80% methanol and total alkaloids extracts exhibited pronounced antiplasmodial activity against the *P. falciparum* K1 strain with IC_{50} values lower than 0.25 μg/ml (Tshodi et al., 2012). The chloroformic ($IC_{50} = 2.25$ μg/ml) and aqueous acid soluble ($IC_{50} = 8.64$ μg/ml) fractions from the partition of the 80% methanol extract also showed pronounced and good antiplasmodial activity, respectively. The petroleum ether and 80% methanol subfractions from the chloroformic fraction showed IC_{50} values of 1.86 μg/ml and 9.12 μg/ml, respectively. Additionally, the residual aqueous and chloroformic subfractions from the aqueous acid soluble fractions exhibited IC_{50} values of < 0.25 μg/ml and 21.50 μg/ml, respectively.

In a follow up study, the aqueous, ethanol, ethyl acetate, n-hexane and dichloromethane extracts from *B. sumatrana* seeds were evaluated against a Congolese chloroquine-sensitive strain of *P. falciparum*. Results indicated that the aqueous, ethanol and ethyl acetate extracts exhibited pronounced antiplasmodial activity with IC_{50} values of 0.40 μg/ml, 0.35 μg/ml and < 0.02 μg/ml, respectively. By contrast, the n-hexane and dichloromethane extracts were inactive ($IC_{50} > 100$ μg/ml) (Penge et al., 2013).

Mbenza et al. (2012) investigated the antiplasmodial activity of different extracts, fractions and subfractions from the leaves, stem bark and root bark of *Strychnos variabilis* against the K1 strain of *P. falciparum*. Results indicated that the aqueous extract from the

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Table 1
Extracts and fractions with pronounced antiplasmodial activity.

	Plant species	Family	Plant part tested	Extract	Biological assay	Pf strain	IC50 (μg/ml)	SI	Other traditional uses	Ref
1	*Alchornea cordifolia* (Schumach.) Muell. Arg.	Euphorbiaceae	Leaves	Aqueous	pLDH	K1	4.84	> 13.2	Cough, bronchitis, angina, diarrhea, intestinal parasites, dysentery, headache, fever, aphrodisiac, sprains or fractures	Muganza et al. (2012)
			Leaves	MeOH	pLDH	Ghana	2.8 ± 0.6	> 22.8		Mesia et al. (2008)
2	*Alstonia congensis* Engl. *(Synonym : Alstonia gilletii* DeWild.*)*	Apocynaceae	Leaves	MeOH	pLDH	K1	5.12	6.47	Stomach cramps, diarrhea, hernia, worms, galactogogue, emetic, spleen diseases, fever	Lumpu et al. (2013)
			Leaves	Aqueous	pLDH	K1	2.55	> 25.10		Lumpu et al., 2013
			Leaves	Alkaloid	pLDH	K1	2.15	3.93		Lumpu et al. (2013)
			Root bark	MeOH	pLDH	K1	5.84	> 10.96		Lumpu et al. (2013)
			Root bark	Aqueous	pLDH	K1	2.04	> 31.37		Lumpu et al. (2013)
										Lumpu et al. (2013)
			Root bark	Alkaloid	pLDH	K1	2.17	> 29.49		Lumpu et al. (2013)
			Stem bark	MeOH	pLDH	K1	2.21	10.18		Lumpu et al. (2013)
			Stem bark	Aqueous	pLDH	K1	2.15	> 29.76		Lumpu et al. (2013)
			Stem bark	Alkaloid	pLDH	K1	3.64	> 17.58		
3	*Anisopappus chinensis* (L.) Hook. f. &Arn.	Asteraceae	Whole plant	MeOH	pLDH	3D7	8.82	14.32	Inflammation, gastric ulcer, fever	Lusakibanza et al. (2010)
			Whole plant	Dichlor	pLDH	3D7	6.53	15.05		Lusakibanza et al. (2010)
			Whole plant	MeOH	pLDH	W2	12.24	10.32		Lusakibanza et al. (2010)
			Whole plant	Dichlor	pLDH	W2	6.37	15.42		Lusakibanza et al. (2010)
4	*Brucea sumatrana* Roxb. *(Synonym : Brucea javanica* (L.) Merr.*)*	Simaroubaceae	Seeds	Aqueous	Parasite growth	Clin Isol	0.6	125	Amebic dysentery, diarrhea	Penge et al. (2013)
			Seeds	Ethanol	Parasite growth	Clin Isol	< 0.6	142.8		Penge et al. (2013)
			Seeds	Ethylacetate	Parasite growth	Clin Isol	< 0.02	2500		Penge et al. (2013)
			Seeds	MeOH	pLDH	K1	< 0.25	2.16		Tshodi et al. (2012)
			Seeds	Aqueous	pLDH	K1	< 0.25	6.2		Tshodi et al. (2012)
			Seeds	Alkaloid	pLDH	K1	< 0.25	1.72		Tshodi et al. (2012)
5	*Cassia occidentalis* L. *(Synonym : Senna occidentalis* (L.) Link*)*	Caesalpiniaceae	Leaves	EtOH or Dichlor	Parasite growth	Clin Isol	< 6		Stomach pain, gonorrhea, hemorrhoids, purgative, anemia, fever	Tona et al. (1999)
			Leaves	Petroleum ether	Parasite growth	Clin Isol	1.5 ± 0.7			Tona et al. (2004)
			Leaves	EtOH	Parasite growth	Clin Isol	2.8			Tona et al. (2004)
6	*Celosia trigyna* L. *(Synonym: Celosia digyna* Suess.*)*	Amaranthaceae	Herbal parts	Dichlor	^{3}H-hypoxanthine	D6	5		Intestinal worms, headache, nose inflammation, pain during pregnancy, uterus pain	Ndaya Tshibangu et al. (2002)
7	*Cissampelos mucronata* A. Rich.	Menispermaceae	Root	Ethyl acetate	^{3}H-hypoxanthine	D6	2.9		Cough, conjunctivitis, sexually transmitted diseases, snake bit, fever	Ndaya Tshibangu et al. (2002)
			Root	MeOH	^{3}H-hypoxanthine	D6	1.5			Ndaya Tshibangu et al. (2002)
8	*Croton mubango* Müll. Arg	Euphorbiaceae	Stem bark	MeOH	Parasite growth	Clin Isol	< 0.6		Blennorrhea, splenomegaly, tuberculosis, constipation, fever	Mesia et al. (2005)
			Stem bark	Dichlor	Parasite growth	Clin Isol	< 0.1			Mesia et al. (2005)
			Stem bark	Alkaloid	Parasite growth	Clin Isol	< 0.1			Mesia et al. (2005)
			Stem bark	Aqueous	Parasite growth	Clin Isol	3.2			Mesia et al. (2005)

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Table 1 (*continued*)

	Plant species	Family	Plant part tested	Extract	Biological assay	Pf strain	IC50 (μg/ml)	SI	Other traditional uses	Ref
9	*Cryptolepis sanguinolenta* (Lindl.) Schlechter	Periplocaceae	Root bark	EtOH or Dichlor	Parasite growth	Clin Isol	< 6		Amebiasis, respiratory and urinary tract infectious, rheumatism, gastro-intestinal disorders	Tona et al. (1999)
10	*Enantia chlorantha* Oliv.	Annonaceae	Stem bark	Aqueous	pLDH	K1	7.77	0.7	Sexual asthenia, intestinal worms, intestinal spasms	Muganza et al. (2012)
11	*Entandrophragma palustre* Staner	Meliaceae	Sterm bark	MeOH	pLDH	3D7	15.84	–	Inflammation, fever	Lusakibanza et al. (2010)
			Sterm bark	Dichlor	pLDH	3D7	17.69	–		Lusakibanza et al. (2010)
12	*Epinetrum villosum* (Exell.)Troupin	Menispermaceae	Root	Aqueous	^{3}H-hypoxanthine	FcB1	0.21	27.5	Diarrhea, dysentery	Muganga Otshudi et al. (2005)
13	*Euphorbia hirta* L.	Euphorbiaceae	Whole plant	EtOH or Dichlor	Parasite growth	Clin Isol	< 6		Asthma, diarrhea, amebiasis	Tona et al. (1999)
			Whole plant	Petroleum ether	Parasite growth	Clin Isol	1.2 ± 0.3			Tona et al. (2004)
			Whole plant	EtOH	Parasite growth	Clin Isol	2.4			Tona et al. (2004)
14	*Garcinia kola* Heckel	Clusiaceae	Seeds	EtOH or Dichlor	Parasite growth	Clin Isol	< 6		Diarrhea, aphrodisiac, hypertension, fever	Tona et al. (1999)
			Stem bark	EtOH or Dichlor	Parasite growth	Clin Isol	< 6			Tona et al. (1999)
			Stem bark	Petroleum ether	Parasite growth	Clin Isol	1.6 ± 0.2			Tona et al. (2004)
			Stem bark	EtOH	Parasite growth	Clin Isol	2.9			Tona et al. (2004)
15	*Harungana madagascariensis* Poir.	Clusiaceae	Stem bark	Aqueous	pLDH	K1	9.64	2.1	Anemia, veneral diseases, nephrosis, gastrointestinal disorders, fever	Muganza et al. (2012)
16	*Isolona hexaloba* Engl. & Diels	Annonaceae	Stem bark	Aqueous	pLDH	K1	15.28	2.1	Loss of appetite, rheumatism, intestinal cramps, headache, back pains, sexual weakness	Muganza et al. (2012)
17	*Lantana camara*L.	Verbenaceae	Leaves	MeOH	pLDH	Ghana	12.0 ± 2.2	3.1	Cough, asthma, pharyngitis, colds, chest and intercostals pain, stomach pain, constipation	Mesia et al. (2008)
18	*Microdesmis puberula* Hoof. f.ex Planch *(Synonym: Microdesmis zenkeri* Pax*)*	Pandaceae	Leaves	MeOH	pLDH	Ghana	9.0 ± 1.2	> 7.1	diarrhea, abscesses, gonorrhea, gastrointestinal disorders, colics, aphrodisiac, otitis, ulcers, ovarian troubles, feverish stiffness	Mesia et al. (2008)
19	*Morinda lucida* Benth.	Rubiaceae	Leaves	EtOH	Parasite growth	Clin Isol	5.7		Trypanosomiasis, leishmaniasis	Cimanga et al. (2006)
			Leaves	Dichlor	Parasite growth	Clin Isol	4.2			Cimanga et al. (2006)
			Leaves	EtOH or Dichlor	Parasite growth	Clin Isol	< 6			Tona et al. (1999)
20	*Morinda morindoides* (Baker) Milne-Redhead	Rubiaceae	Leaves	Petroleum ether	Parasite growth	Clin Isol	1.8 ± 0.2		Amebiasis, hemorrhoids, intestinal worms, gonorrhea, rheumatism, tonic, fever	Tona et al. (2004)
			Leaves	EtOH: -petroleum ether fraction	Parasite growth	Clin Isol	1.8 ± 0.2			Cimanga et al. (2009)
				-isoamylic alcohol fraction	Parasite growth	Clin Isol	15.3 ± 3.6			
				-chloroforme fraction	Parasite growth	Clin Isol	8.8 ± 2.5			
21	*Myrianthus arboreus* P. Beauv.	Urticaceae	Bark	Dichlor	^{3}H-hypoxanthine	D6	2.6		Cough, fever	Ndaya Tshibangu et al. (2002)
			Bark	MeOH	^{3}H-hypoxanthine	D6	9.4			Ndaya Tshibangu et al. (2002)

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Table 1 (*continued*)

	Plant species	Family	Plant part tested	Extract	Biological assay	Pf strain	IC50 (μg/ml)	SI	Other traditional uses	Ref
22	*Nauclea pobeguinii* (Pob. ex. Pell.) Petit *(Synonym: Sarcocephalus pobeguinii* Pob. ex. Pell.*)*	Rubiaceae	Stem bark	MeOH	Parasite growth	Clin Isol	3.3		Intestinal worms, abdominal pains, sexual asthenia, gonorrhea	Mesia et al. (2005)
				Dichlor	Parasite growth	Clin Isol	<0.1			Mesia et al. (2005)
				Alkaloid	Parasite growth	Clin Isol	0.6			Mesia et al. (2005)
				Aqueous	Parasite growth	Clin Isol	5.3			Mesia et al. (2005)
23	*Ocimum gratissimum* L.	Lamiaceae	Whole plant	MeOH	pLDH	Ghana	6.0 ± 2.5	2	Headache, rheumatism, hemorrhoids, anthelmintic, upper respiratory tract infections, asthma, pneumonia, fever	Mesia et al. (2008)
				Aqueous	pLDH	K1	7.25	>8.8		Muganza et al. (2012)
24	*Otiophora puciflora* Baker	Rubiaceae	Herbal parts	Dichlor	^{3}H-hypoxanthine	D6	8.7		Cough, psychological disturbances, abortion,	Ndaya Tshibangu et al. (2002)
25	*Phyllantus niruri* L.	Euphorbiaceae	Whole plant	EtOH or Dichlor	Parasite growth	Clin Isol	<6		Dysentery, intestinal spasms, inflammation, fever	Tona et al. (1999)
			Whole plant	Petroleum ether	Parasite growth	Clin Isol	1.3 ± 0.3			Tona et al. (2004)
			Whole plant	EtOH	Parasite growth	Clin Isol	2.5			Tona et al. (2004)
			Whole plant	EtOH	Parasite growth	Clin Isol	2.5			Cimanga et al. (2004)
				-dichlor fraction	Parasite growth	Clin Isol	1.3			
				-isoamylic alcohol fraction	Parasite growth	Clin Isol	2.3			
			Fresh apical stem	EtOH	Parasite growth	Clin Isol	18.2			Cimanga et al. (2004)
			Callus culture (from fresh apical stem)	EtOH	Parasite growth	Clin Isol	16.3			Cimanga et al. (2004)
26	*Physalis angulata* L. *(Synonym : Physalis capsicifolia* Dunal*)*	Solanaceae	Whole plant	MeOH	pLDH	3D7	1.27	12.35	hepatite, diabete,intestinalcramps, inflammation, fever	Lusakibanza et al. (2010)
			Whole plant	Dichlor	pLDH	3D7	1.96	4		Lusakibanza et al. (2010)
										Lusakibanza et al. (2010)
			Whole plant	MeOH	pLDH	W2	3.02	5		Lusakibanza et al. (2010)
			Whole plant	Dichlor	pLDH	W2	2.00	4		Mangwala Kimpende et al. (2013)
			Whole plant	Aqueous	pLDH	3D7	11.36	4.96		Mangwala Kimpende et al. (2013)
			Whole plant	50% EtOH	pLDH	3D7	9.05	4.02		
27	*Piptadeniastrum africanum* (Hook.f.) Brenan	Leguminosae	Stem bark	Aqueous	pLDH	K1	6.11	1.4	Back pain, intestinal cramps, constipation, sexual asthenia	Muganza et al. (2012)
28	*Polyalthia suaveolens* Engl. & Diels	Annonaceae	Stem bark	MeOH	pLDH	Ghana	<1.0	>64	Gastritis, diarrhea, snakebite, sexual weakness, dermatose, fever, intestinal spasms	Mesia et al. (2008)
29	*Polyscias fulva* (Hierns) Harms	Araliaceae	Bark	Dichlor	^{3}H-hypoxanthine	D6	9.8		Mental illness, fever	Ndaya Tshibangu et al. (2002)
30	*Pyrenacantha staudtii* Engl.	Icacinaceae	Leaves	Dichlor	Parasite growth	Clin Isol	<0.1		Spasms, intestinal worms	Mesia et al. (2005)
			Leaves	Aqueous	Parasite growth	Clin Isol	15.2			Mesia et al. (2005)

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Table 1 (*continued*)

	Plant species	Family	Plant part tested	Extract	Biological assay	Pf strain	IC50 (μg/ml)	SI	Other traditional uses	Ref
31	*Quassia africana* Baill.	Simaroubaceae	Root bark	Aqueous	pLDH	K1	0.46	13.7	Gastrointestinal affections, hypertension, blenorragia, hernia, rheumatism, headache, toothachebroncho-pneumonia, angina, hemorrhoids, diarrhea, wounds, scabies, fever	Muganza et al. (2012)
			Stem bark	Aqueous	pLDH	K1	1.27	13.6		Muganza et al. (2012)
32	*Sapium cornutum* Pax	Euphorbiaceae	Stem bark	MeOH	pLDH	Ghana	2.0 ± 0.3	18.5	Hernia, scurvy, stomatitis, anthelmintic, purgative	Mesia et al. (2008)
33	*Strychnos icaja* Baill.	Loganiaceae	Root bark	MeOH	pLDH	3D7	0.69	–	Ordeal poison	Lusakibanza et al. (2010)
			Root bark	Dichlor	pLDH	3D7	0.84	–		Lusakibanza et al. (2010)
			Root bark	MeOH	pLDH	W2	0.42	–		Lusakibanza et al. (2010)
			Root bark	Dichlor	pLDH	W2	0.61	–		Lusakibanza et al. (2010)
34	*Strychnos variabilis* De Wild.	Loganiaceae	Leaves	Alkaloid	pLDH	K1	7.88	8.1	Sleeping sickness	Mbenza et al. (2012)
			Root bark	MeOH	pLDH	K1	5.66	11.3		
			Root bark	Alkaloid	pLDH	K1	9.60	6.7		
			Stem bark	MeOH	pLDH	K1	5.66	1		
			Stem bark	Alkaloid	pLDH	K1	4.69	6.5		
35	*Tetracera poggei* Gilg.	Dilleniaceae	Leaves	Petroleum ether	Parasite growth	Clin Isol	1.7 ± 0.4		Dysentery, hepatitis, blennorrhagia, diuretic, fever	Tona et al. (2004)
36	*Triclisia gilletii* (De Wild) Staner *(Synonym: Triclisia dictyophilla* Diels*)*	Menispermaceae	Leaves	Aqueous	pLDH	K1	5.13	> 12.5	Rheumatism, dysentery, abdominal pains, diarrhea, anthelmintic, cough, fits, veneral diseases, fever	Muganza et al. (2012)
			Stem bark	MeOH	pLDH	Ghana	2.0 ± 0.3	17		Mesia et al. (2008)
			Leaves	MeOH	pLDH	K1	0.64	> 100		Kikueta et al. (2013)
			Leaves	Aqueous	pLDH	K1	0.43	11.14		Kikueta et al. (2013)
			Leaves	Alkaloid	pLDH	K1	0.34	8.14		Kikueta et al. (2013)
			Root bark	MeOH	pLDH	K1	0.75	7.39		Kikueta et al. (2013)
			Root bark	Aqueous	pLDH	K1	1.67	3.40		Kikueta et al. (2013)
			Root bark	Alkaloid	pLDH	K1	0.25	1.20		Kikueta et al. (2013)
			Stem bark	MeOH	pLDH	K1	0.75	9.77		Kikueta et al. (2013)
			Stem bark	Aqueous	pLDH	K1	1.25	3.80		Kikueta et al. (2013)
			Stem bark	Alkaloid	pLDH	K1	1.67	16.44		Kikueta et al. (2013)
			Leaves	MeOH	Parasite growth	Clin Isol	< 0.02	> 3200		Kikueta et al. (2013)
			Leaves	Aqueous	Parasite growth	Clin Isol	1.55	3.09		Kikueta et al. (2013)
			Leaves	Alkaloid	Parasite growth	Clin Isol	< 0.02	> 138.50		Kikueta et al. (2013)
			Root bark	MeOH	Parasite growth	Clin Isol	< 0.02	> 275		Kikueta et al. (2013)
			Root bark	Aqueous	Parasite growth	Clin Isol	< 0.02	> 212		Kikueta et al. (2013)
			Root bark	Alkaloid	Parasite growth	Clin Isol	< 0.02	> 100		Kikueta et al. (2013)
			Stem bark	MeOH	Parasite growth	Clin Isol	1.15	6.37		Kikueta et al. (2013)
			Stem bark	Aqueous	Parasite growth	Clin Isol	< 0.02	> 317		Kikueta et al. (2013)
			Stem bark	Alkaloid	Parasite growth	Clin Isol	< 0.02	> 205		Kikueta et al. (2013)
37	*Vernonia amygdalina* Delile (Synonym: *Vernonia giorgii* De Wild.)	Compositae	Leaves	Petroleum ether	Parasite growth	Clin Isol	2.5 ± 0.7		Platelet aggregation, antimicrobial	Tona et al. (2004)
			Leaves	EtOH	Parasite growth	Clin Isol	9.7			Tona et al. (2004)

Table 2
Extracts and fractions with moderate or weak antiplasmodial activity.

Plant species	Family	Plant part tested	Extract	Biological assay	Pf strain	IC50 (μg/ml)	References
Afrostyrax lepidophyllus Mildbr.	Huaceae	Root bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Alchornea floribunda Müll. Arg.	Euphorbiaceae	Leaves	Aqueous	pLDH	K1	20.8	Muganza et al. (2012)
		Root bark	MeOH	pLDH	Ghana	34.0 ± 3.6	Mesia et al. (2008)
Alstonia boonei De Wild.	Apocynaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
		Stem bark	MeOH	pLDH	Ghana	40.0 ± 4.3	Mesia et al. (2008)
Alstonia congensis Engl. (Synonym: *Alstonia gilletii* De Wild.)	Apocynaceae	Stem bark	MeOH	pLDH	Ghana	50.0 ± 5.3	Mesia et al. (2008)
Amorphophallus bequaertii De Wild.	Araceae	Tuber	Aqueous	^{3}H-hypoxanthine	D6 and W2	> 10	Ndaya Tshibangu et al. (2002)
		Tuber	MeOH	^{3}H-hypoxanthine	D6 and W2	> 10	Ndaya Tshibangu et al. (2002)
		Tuber	Dichlor	^{3}H-hypoxanthine	D6 and W2	> 10	Ndaya Tshibangu et al. (2002)
Anonidium mannii (Oliv.) Engl. & Diels	Annonaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Autranella congolensis (De Wild.) A. Chev.	Sapotaceae	Stem bark	Aqueous	pLDH	K1	35.45	Muganza et al. (2012)
Calycobolus sp	Convolvulaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Canthium oddonii (De Wild.) C.M. Evrard *(Synonym: Psydrax palma* (K.Schum.) Bridson*)*	Rubiaceae	Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Cassia floribunda Collad.	Leguminosae	Root bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Cassia hirsuta L. *(Synonym: Senna hirsuta* (L.) H.S. Irwin & Barneby)	Leguminosae	Root bark	MeOH	pLDH	Ghana	32.0 ± 1.8	Mesia et al. (2008)
Cassia occidentalis L. *(Synonym: Senna occidentalis* (L.) Link*)*	Leguminosae	Leaves	EtOH	^{3}H-hypoxanthine	FCM 29	16+- 16.0 +- 2.6	Ngbolua et al. (2011b)
Citrus aurantium L. (Synonym: *Citrus amara* Link)	Rutaceae	Leaves	MeOH	pLDH	Ghana	40.0 ± 2.1	Mesia et al. (2008)
Crossopteryx febrifugA (Afzel.) Benth.	Rubiaceae	Leaves	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Cymbopogon citratus (DC.) Stapf	Poaceae	Leaves	MeOH	pLDH	Ghana	42.0 ± 2.2	Mesia et al. (2008)
Cymbopogon densiflorus (Steud.) Stapf (Synonym: *Andropogon densiflorus* Steud.)	Poaceae	Whole plant	MeOH	pLDH	Ghana	25.0 ± 2.7	Mesia et al. (2008)
Dalhousiea africana S. Moore	Leguminosae	Leaves	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Dichostemma glaucescens Pierre	Euphorbiaceae	Stem bark	MeOH	pLDH	Ghana	44.0 ± 2.7	Mesia et al. (2008)
Drypetes gossweileri S. Moore	Euphorbiaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
		Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Garcinia kola Heckel	Clusiaceae	Fruit	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Garcinia punctata Oliv.	Clusiaceae	Stem bark	Aqueous	pLDH	K1	36.56	Muganza et al. (2012)
Guibourtia demeusei (Harms) J. Leonard (Synonym: *Copaifera demeusei* Harms)	Leguminosae	Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Hymenocallis senegambica Kunth & C.D. Bouché *(Synonym: Hymenocallis littoralis* (Jacq.) Salisb.	Amaryllidaceae	Leaves	MeOH	pLDH	Ghana	32.0 ± 2.1	Mesia et al. (2008)
Jatropha curcas L.	Euphorbiaceae	Root bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Landolphia owariensis P. Beauv. *(Synonym: Landolphia droogmansiana* De Wild*)*	Apocynaceae	Leaves	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Luffa cylindrical (L.) M. Roem.	Cucurbitaceae	Leaves	MeOH	pLDH	Ghana	33.0 ± 1.8	Mesia et al. (2008)
Mammea africana Sabine *(Synonym: Garcinia golaensis* Hutch. & Dalziel*)*	Calophyllaceae	Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
		Stem bark	Aqueous	pLDH	K1	28.57	Muganza et al. (2012)
Manniophyton fulvum Müll. Arg. *(Synonym: Manniophyton tricuspe* Pierre ex A. Chev.)	Euphorbiaceae	Leaves	Aqueous	pLDH	K1	22.44	Muganza et al. (2012)
		Root bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
		Stem bark	Aqueous	pLDH	K1	51.71	Muganza et al. (2012)

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Table 2 (*continued*)

Plant species	Family	Plant part tested	Extract	Biological assay	Pf strain	IC50 (μg/ml)	References
Manotes pruinosa Gilg. *(Synonym: Manotes expansa* Sol. ex Planch.*)*	Connaraceae	Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Massularia acuminata (G. Don) Bullock ex Hoyle *(synonym: Massularia capitata* (Hook.) Schljakov)	Rubiaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Momordica charantia L. *(Synonym: Cucumis argyi* H. Lév)	Cucurbitaceae	Whole plant	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Morinda citrifolia L. *(Synonym: Morinda asperula* Standl.*)*	Rubiaceae	Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Morinda morindoides (Baker) Milne-Redh. *(Synonym: Gaertnera morindoides* Baker)	Rubiaceae	Leaves	EtOH	Parasite growth	Clin Isol	60–200	Tona et al. (1999)
		Leaves	Dichlor	Parasite growth	Clin Isol	> 100	Tona et al. (1999)
		Leaves	EtOH	Parasite growth	Clin Isol	94.2 ± 3.4	Tona et al. (2004)
Musanga cecropioides R. Br. ex Tedlie	Urticaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Napoleona vogelii Hook. & Planch.	Lecythidaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Omphalocarpum agglomeratum De Wild.	Sapotaceae	Root bark	MeOH	pLDH	Ghana	32.0 ± 3.3	Mesia et al. (2008)
Ongokea gore (Hua) Pierre	Olacaceae	Stem bark	MeOH	pLDH	Ghana	32.0 ± 3.2	Mesia et al. (2008)
Penianthus longifolius (Miers) *(Synonym: Penianthus fruticosus* Hutch. & Dalziel)	Menispermaceae	Root bark	Aqueous	pLDH	K1	27.1	Muganza et al. (2012)
Pentaclethra eetveldeana De Wild. & T. Durand *(Synonym: Pentaclethra filiformis* A. Chev.*)*	Leguminosae	Root bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Phytolacca dodecandra L'Hér.	Phytolaccaceae	Leaves	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Picralima nitida (Stapf) T. Durand & H. Durand *(Synonym: Picralima klaineana* Pierre*)*	Apocynaceae	Stem bark	Aqueous	pLDH	K1	36.76	Muganza et al. (2012)
Piper guineense Schumach. & Thonn *(Synonym: Piper clusii* (Miq.) C. DC.*)*	Piperaceae	Leaves	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Piptadenia africana Hook. f. *(Synonym: Piptadeniastrum africanum* (Hook. f.) Brenan*)*	Leguminosae	Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Plumbago zeylanica L. *(Synonym: Plumbago scandens* L.*)*	Plumbaginaceae	Leaves	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Polyalthia suaveolens Engl. & Diels *(Synonym: Greenwayodendron suaveolens* (Engl. & Diels) Verdc.)	Annonaceae	Root bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
		Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Psorospermum febrifugum Spach *(Synonym: Psorospermum ferrugineum* Hook. f.)	Hypericaceae	Leaves	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Pyrenacantha klaineana Pierre ex Exell & Mendonça	Icacinaceae	Leaves	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Rauwolfia vomitoria Afzel.	Apocynaceae	Leaves	MeOH	pLDH	Ghana	35.0 ± 2.1	Mesia et al. (2008)
Rubus rigidus Sm. *(Synonym: Rubus mundtii* Cham. & Schltdl)	Rosaceae	Root	MeOH	^{3}H-hypoxanthine	D6 and W2	> 10	Ndaya Tshibangu et al. (2002)
		Root	Dichlor	^{3}H-hypoxanthine	D6 and W2	> 10	Ndaya Tshibangu et al. (2002)
Scorodophloeus zenkeri Harms	Leguminosae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
		Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Staudtia kamerunensis Warb.	Myristicaceae	Stem bark	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
Tetracera alnifolia Willd. *(Synonym: Tetracera djalonica* A. Chev. ex Hutch & Dalziel*)*	Dilleniaceae	Leaves	MeOH	pLDH	Ghana	39.0 ± 2.5	Mesia et al. (2008)
Tetracera poggei Gilg *(Synonym: Tetracera malangensis* Exell*)*	Dilleniaceae	Leaves	EtOH	Parasite growth	Clin Isol	36.9 ± 4.2	Tona et al. (2004)
		Leaves	EtOH	Parasite growth	Clin Isol	20–60	Tona et al. (1999)
		Leaves	Dichlor	Parasite growth	Clin Isol	> 100	Tona et al. (1999)
Tetrapleura tetraptera (Schum. & Thonn) Taub. *(Synonym: Adenanthera tetraptera* Schum. & Thonn.)	Leguminosae	Fruit	Aqueous	pLDH	K1	> 64	Muganza et al. (2012)
		Stem bark	Aqueous	pLDH	K1	33.87	Muganza et al. (2012)

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Table 2 (*continued*)

Plant species	Family	Plant part tested	Extract	Biological assay	Pf strain	IC50 (μg/ml)	References
Thomandersia hensii De Wild. & T. Durand	Schlegeliaceae	Leaves	Aqueous	pLDH	K1	41.12	Muganza et al. (2012)
Thomandersia laurifolia (T. Anderson ex Benth.) Baill.	Schlegeliaceae	Stem bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Trema guineensis (Schum. & Thonn) Ficalho *(Synonym: Trema orientalis* (L.) Blume	Cannabaceae	Root bark	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Tridax procumbens (L.) L. *(Synonym: Balbisia elongata* Willd)	Compositae	Leaves	MeOH	pLDH	Ghana	> 64	Mesia et al. (2008)
Vernonia amygdalina Delile	Compositae	Leaves	EtOH	Parasite growth	Clin Isol	6–20	Tona et al. (1999)
		Leaves	Dichlor	Parasite growth	Clin Isol	> 100	Tona et al. (1999)

root bark and stem bark showed moderate antiplasmodial activity while that from the leaves was inactive. The 80% methanol extract from the root bark, stem bark and leaves exhibited IC_{50} values of 5.66 μg/ml, 11.76 μg/ml and > 64 μg/ml, respectively. The chloroform soluble fraction from the partition of the 80% methanol extract of the leaves (IC_{50} = 4.81 μg/ml) and stem bark (IC_{50} = 5.74 μg/ml) as well as the acid aqueous soluble fraction from the partition of the 80% methanol extract of all plant parts (IC_{50} = 3.17–4.23 μg/ml) showed pronounced antiplasmodial activity. The total alkaloid extracts from all plant parts also exhibited IC_{50} values ranged between 4.69 μg/ml and 9.60 μg/ml.

In another work conducted in our laboratory, the aqueous and 80% methanol extracts of *Diodia sarmentosa* leaves (Jobalo, 2013) were submitted to *in vitro* antiplasmodial activity against a Congolese *P. falciparum* strain sensitive to quinine and isolated clinically. The obtained results indicated that both extracts showed pronounced antiplasmodial activity with IC_{50} < 5 μg/ml. In the same way, the chloroform, ethyl acetate, n-butanol and residual aqueous phase from the partition of the 80% methanol extract were also found to exhibit antiplasmodial activity against this *P.* strain at different extents (IC_{50} < 10 μg/ml).

Following previous studies performed by Tona et al. (1999, 2004), Cimanga et al. (2004) compared the chemical composition and the antiplasmodial activity of callus extracts obtained after different times of cultivation to that of the intact fresh apical stem and whole plant extracts as well as fractions of *P. niruri*. Based on their results, the authors concluded that the callus cultures of fresh apical stems can produce secondary metabolites with some antiplasmodial activity. The activity of the ethanolic extract of a 1-month-old callus culture (IC_{50} = 16.3 μg/ml) was higher than the ethanolic extracts of the fresh apical stem (IC_{50} = 18.2 μg/ml) but lower than that of the ethanolic extract and fractions (dichloromethane and isoamylic alcohol) from the whole plant of *P. niruri* (IC_{50} < 3 μg/ml). These results were in good agreement with those obtained previously by Luyindula et al. (2004).

In another study, calli from fresh apical stems of *P. amarus* were also bioassayed. The callus cultures were induced in Murashige and Skoog medium supplemented with different proportions of indole-butyric acid (IBA), benzylaminopurine (BAP) and mannitol (Musuamba et al., 2010). The ethanol extract from callus cultivated with IBA/BAP/Mannitol 1:1:0.5% exhibited the most interesting activity (IC_{50} < 0.19 μg/ml). This activity was higher than that of ethanol extracts from whole plant (IC_{50} = 2.5 μg/ml) and intact apical stem (IC_{50} = 8.2 μg/ml) of the same species.

In the light of all the studies conducted to date with Congolese antimalarial plants, a number of solvents were used to obtain crude extracts and fractions. These extractive solvents include methanol (37%), aqueous (27%), ethanol (13%), dichloromethane (13%) and total alkaloids (6%), among others which can contain active lead compounds. Even though aqueous extracts (decoction, macerate or infusion) represent the typical preparation of Congolese traditional health practitioners (Kambu, 1990), organic extracts were mainly used in assessing the antiplasmodial activity of Congolese medicinal plants. This trend may be explained by the complexity and difficulty in developing a suitable workup procedure with aqueous extracts (Rasoanaivo et al., 2004). However, it is reported that the organic extracts were generally more active *in vitro* than the aqueous extracts (Jansen et al., 2010; Bero et al., 2009; Mbatchi et al., 2006; Lusakibanza et al., 2010). Therefore, in further screening programs of Congolese antimalarial plants used traditionally, both aqueous and organic extracts should be bioassayed as far as possible.

Among the tested extracts, about 120 of them presented promising activity against *P. falciparum* culture-adapted strains (65%) or clinical isolates from the DR Congo (35%) (Table 1). On the whole, 47%, 35% and 18% of these plant extracts were bioassayed by the pLDH activity, the schizont maturation method and the [^{3}H]-hypoxanthine test, respectively. However, only extracts and fractions from *T. gilletii* (Kikueta et al., 2013), *B. sumatrana* (Penge et al., 2013; Tshodi et al., 2012) and *N. pobeguinii* (Mesia et al., 2005, 2010a) were tested against both clinical isolates (schizont maturation method) and laboratory strains (pLDH assay). It was found that, for most of these samples, the IC_{50} values against the clinical isolates were lower than those observed against the selected laboratory strains (K1 or Ghana). Such comparison can be made because a 48 h incubation period was proposed for the schizont maturation test (Tona et al., 1999) thereby making it applicable to most blood schizontocidal plant-derived products. However, at this stage of experiments, no general relationship can be establish between levels of activity, parasite strains tested and *in vitro* methods used. Consequently, further complementary studies are needed in this field.

On the other hand, studies dedicated to the investigation of the antiplasmodial properties of leaf (30%) and stem bark (30%) plant materials constitute the most common followed by root bark (22%), whole plant (11%), herbal (4%) and seed (2%) plant materials. This trend may be explained by the fact that root bark and stem bark constitute the main raw materials for preparing remedies to treat malaria in Congolese folk medicine (Kambu, 1990). Unfortunately, numerous harvests of roots are destructive for the plants. Hence, the use and antiplasmodial investigations of plant materials that are less damaging to plant stocks should be encouraged. To this end, the *in vitro* antiplasmodial activity of extracts (and fractions) from the leaves, stem bark and root bark of *T. gilletii* (Kikueta et al., 2013), *A. congensis* (Lumpu et al., 2013) and *S. variabilis* (Mbenza et al., 2012) were evaluated and compared. The results indicated that extracts from the leaves of these three plants exhibited IC_{50} values in the same range than those from the

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stem bark and root bark. These data are encouraging; nevertheless, further investigations with other plant species should be performed to generalize or not these observations.

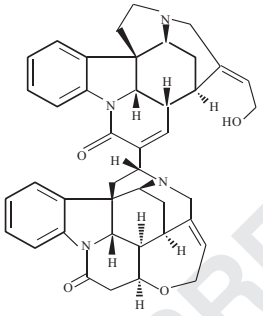
2.2. In vitro antiplasmodial activity of isolated compounds

Besides *in vitro* antiplasmodial studies performed on crude extracts and fractions of Congolese plants, phytochemical analysis and bioassay-guided fractionation were also conducted leading to the isolation of several molecules that have antiplasmodial properties. For the isolation of alkaloids, flavonoids, anthraquinones and terpenoids, the general procedure described in the literature was carried out (Harborne, 1998) while the bioguided fractionation was made either by column chromatography, preparative thin layer chromatography or preparative high performance liquid chromatography. The isolated compounds were identified by chemical and spectroscopic methods. Details about these bioactive compounds are given below as well as in Table 3 and Fig. 1.

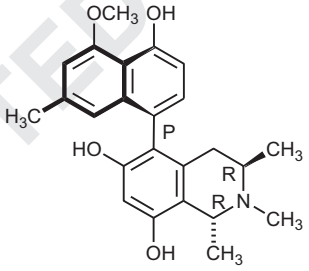
As *M. morindoides* is a medicinal plant widely used in the DR Congo to fight malaria, it was subjected to bioassay-guided fractionation (Cimanga et al., 1995, 1997a, 2003, 2006a). From the 80% methanol extract of the leaves of *M. morindoides*, chrysoeriol 7-neohesperidoside was isolated and identified. Moreover, a series of flavonoids (quercetin, quercetin 7,4'-dimethylether, quercetin 3-rhhamnoside, quercetin 3-rutinoside, luteolin 7-glucoside, apigenin 7-glucoside, kaempferol 3-rhamnoside, kaempferol 3-rutinoside, kaempferol-7-rhamnosylsophoroside and chrysoeriol-7-neohesperidoside) were also isolated for the first time (Cimanga et al., 1995, 2003). Afterwards, two anthraquinones (alizarin and chrysarin) were isolated from the aforementioned extract. Quercetin showed a good antiplasmodial activity (IC_{50}=5.5 μg/ml on NF54/64 strain) while alizarin and chrysarin displayed a moderate activity (IC_{50}=25.3 μg/ml and 14.5 μg/ml on NF54/64 strain, respectively) (Cimanga et al., 2009).

From the 80% methanolic extract of *M. morindoides* leaves, Cimanga et al. also isolated 8 iridoids: gaertneroside, acetylgaertneroside, methoxygaertneroside, epoxygaertneroside, dehydrogaertneroside, dehydromethoxygaertneroside, epoxymethoxygaertneroside and gaertneric acid (Cimanga et al., 2006a, 2009). Some of these iridoids were reported to exhibit *in vitro* antiplasmodial activity against *P. falciparum* CDC1-Gambia (cycloguanil-resistant) with IC_{50} values ranging from 0.04 to 21.9 μM (Tamura et al., 2010) in agreement with previous results (Tasdemir et al., 2005).

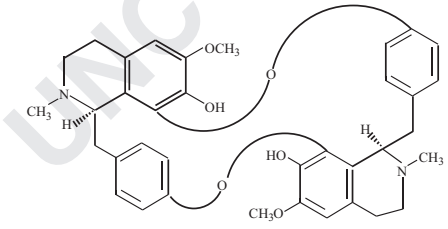
In another bioassay-guided purification, ursolic acid and oleanolic acid, two known triterpenic acids were isolated from the petroleum ether extract of the leaves of *M. lucida* (Cimanga et al., 2006b). Ursolic



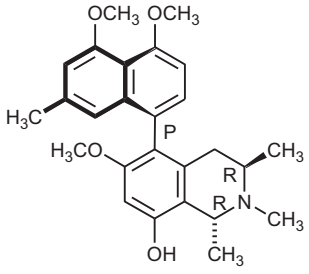
Strychnogucine B



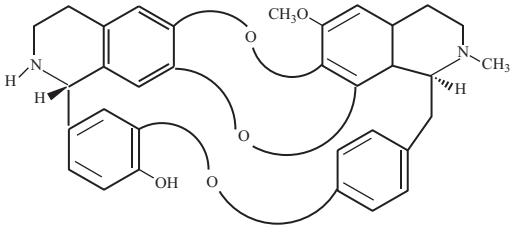
Ancistrocongoline A



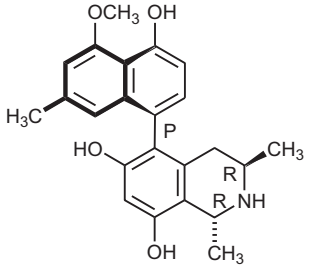
Isochondodendrine



Ancistrocongoline B



Cocsoline



Korupensamine

Fig. 1. Structures of compounds with high activity *in vitro* against various strains of *Plasmodium falciparum* (IC_{50} < 1 μg/ml).

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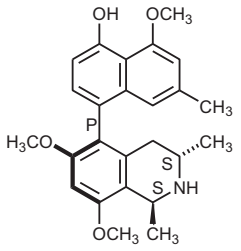
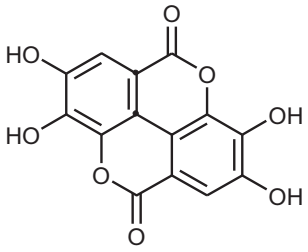
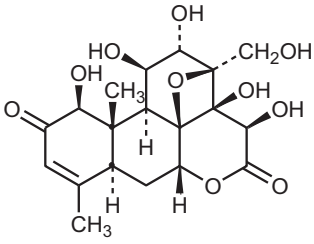


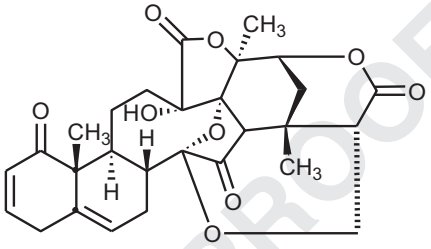
Ancistroealaine B



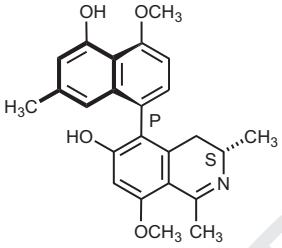
Ellagic acid



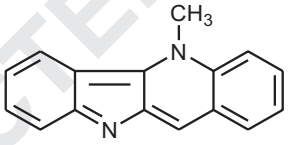
Yadanziolide A



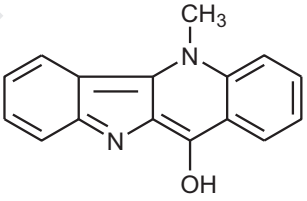
Physalin B



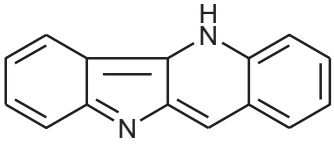
Ancistrolikokine D



Cryptolepine



Hydroxycryptolepine



Neocryptolepine

Fig. 1. (*continued*)

acid and oleanolic acid showed antiplasmodial activity with IC_{50} values of 3.1 and 15.2 μg/ml, respectively, against a Congolese chloroquine-sensitive strain of *P. falciparum*. These values are in the same range than most of data from literature (Lenta et al., 2007; van Baren et al., 2006; Bero et al., 2013). Unfortunately, at 25 μg/ml, the two compounds were found to be inactive against the chloroquine-resistant *P. falciparum* K1 strain. Of note, the petroleum ether, dichloromethane and ethanolic extracts showed growth inhibitory against the same *P. falciparum* clinical isolates with IC_{50} values of 3.9 μg/ml, 5.2 μg/ml and 5.7 μg/ml, respectively.

As mentioned above, the aqueous and 80% ethanolic extracts from the root bark of *C. sanguinolenta* showed potent antiplasmodial activity (Tona et al., 1999). Bioassay-guided fractionation of this 80% ethanolic extract led to the isolation of four alkaloids: quindoline, hydroxycryptolepine, cryptolepine hydrochloride and cryptolepine (Cimanga et al., 1996, 1997b). Interestingly, cryptolepine and its related compounds were reported to exhibit antiplasmodial activities against three strains of *P. falciparum*, namely D6 (IC_{50}=0.027–0.063 μg/ml), K1 (IC_{50}=0.033–0.087 μg/ml) and W2 (IC_{50}=0.041–0.108 μg/ml) (Cimanga et al., 1997b) (see Table 3).

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Table 3
Isolated compounds with pronounced antiplasmodial activity.

Plant species	Family	Plant part Used	Isolated compound	Biological assay	Pf strain	IC50 μg/ml	SI	Reference
Ancistrocladus congolensis J. Léonard	Ancistrocladaceae	Stem, Root bark	Ancistrocongoline A	^{3}H-hypoxanthine	K1	0.214	420	Bringmann et al. (2002)
			Ancistrocongoline B	^{3}H-hypoxanthine	K1	0.158	211	
			Ancistrocongoline C	^{3}H-hypoxanthine	K1	3.002	> 30	
			Ancistrocongoline D	^{3}H-hypoxanthine	K1	1.983	14	
			Korupensamine A	^{3}H-hypoxanthine	K1	0.164	232	
Ancistrocladus ealaensis J. Léonard	Ancistrocladaceae	Leaves, Stem bark, Root bark	Ancistroealaine A	^{3}H-hypoxanthine	K1	1.2	> 75	Bringmann et al. (2000)
			Ancistroealaine B	^{3}H-hypoxanthine	K1	0.52	173.0	
			Ancistroealaine A	^{3}H-hypoxanthine	NF54	4.0	> 22.5	
			Ancistroealaine B	^{3}H-hypoxanthine	NF54	0.79	113.9	
Ancistrocladus likoko J. Léonard	Ancistrocladaeae	Root bark	Ancistrolikokine D	^{3}H-hypoxanthine	K1	0.79	46.3	Bringmann et al. (2003)
			Ancistrolikokine D	^{3}H-hypoxanthine	NF54	1.16	31.5	
Ancistrocladus sp	Ancistrocladaceae	Root bark	5'-*0*-Demethylhamatine	^{3}H-hypoxanthine	K1	1.0	70.2	Bringmann et al. (2008)
			5'-*0*-Demethylhamatinine	^{3}H-hypoxanthine	K1	2.8	29.8	
			6-*0*-Demethylancistroealaine A	^{3}H-hypoxanthine	K1	1.8	> 50	
			6,5'-*0,0*-Didemethylancistroealaine A	^{3}H-hypoxanthine	K1	2.1	> 43	
			5-epi-6-*0*-Methylancistrobertsonine A	^{3}H-hypoxanthine	K1	1.9	35.8	
			5-epi-4'-*0*-Demethylancistrobertsonine C	^{3}H-hypoxanthine	K1	2.6	16.8	
			2-Methyl-4-oxo-4 H-1-benzopyrane 5-carboxylic acid	^{3}H-hypoxanthine	K1	> 5	> 18	
			6-*0*-demethylancistrobrevine A	^{3}H-hypoxanthine	K1	2.1	12.0	
Brucea sumatrana Roxb.	Simaroubaceae	Seeds	Yadanziolide A	Parasite growth	Clin Isol	0.02	25.5	Penge et al. (2013)
			Yadanzioside C	Parasite growth	Clin Isol	5.60	3.6	
			Yadanzioside F	Parasite growth	Clin Isol	3.50	4.6	
Cryptolepis sanguinolenta (Lindl.) Schlechter	Periplocaceae	Root bark	Quindoline	^{3}H-hypoxanthine	D6	0.063		Cimanga et al. (1997b)
			Hydroxycryptolepine	^{3}H-hypoxanthine	D6	0.031		
			Cryptolepine hydrochloride	^{3}H-hypoxanthine	D6	0.041		
			Cryptolepine	^{3}H-hypoxanthine	D6	0.027		
			Quindoline	^{3}H-hypoxanthine	K1	0.087		
			Hydroxycryptolepine	^{3}H-hypoxanthine	K1	0.045		
			Cryptolepine hydrochloride	^{3}H-hypoxanthine	K1	0.062		
			Cryptolepine	^{3}H-hypoxanthine	K1	0.033		
			Quindoline	^{3}H-hypoxanthine	W2	0.108		
			Hydroxycryptolepine	^{3}H-hypoxanthine	W2	0.059		
			Cryptolepine hydrochloride	^{3}H-hypoxanthine	W2	0.052		
			Cryptolepine	^{3}H-hypoxanthine	W2	0.041		

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Table 3 (*continued*)

Plant species	Family	Plant part Used	Isolated compound	Biological assay	Pf strain	IC50 µg/ml	SI	Reference
Cryptolepis sanguinolenta (Lindl.) Schlechter	Periplocaceae	Root bark	Neocryptolepine	^{3}H-hypoxanthine	K1	2.61	> 3	van Miert et al. (2005)
			Biscryptolepine	^{3}H-hypoxanthine	K1	10	> 100	
Epinetrum villosum (Exell.) Troupin	Menispermaceae	Root	Cycleanine	^{3}H-hypoxanthine	FcB1	2.8	118	Longanga Otshudi et al. (2005)
			Cycleanine N-oxide	^{3}H-hypoxanthine	FcB1	8.6	4.9	
			Isochondodendrine	^{3}H-hypoxanthine	FcB1	0.1	175	
			Cocsoline	^{3}H-hypoxanthine	FcB1	0.3	9.3	
Morinda lucida Benth.	Rubiaceae	Leaves	Ursolic acid	Parasite growth	Clin isol	3.1		Cimanga et al. (2006)
			Oleanolic acid	Parasite growth	Clin isol	15.2		
Morinda morindoides (Baker) Milne-Redhead	Rubiaceae	Leaves	Quercetin	^{3}H-hypoxanthine	NF54	5.5		Cimanga et al. (2009)
			Alizarin	^{3}H-hypoxanthine	NF54	25.3		
			Chryzarin	^{3}H-hypoxanthine	NF54	14.5		
Phyllantus amarus Schum. et Thonn.	Euphorbiaceae	Apical stem	Quercetin	Parasite growth	Clin isol	3.2	15.6	Musuamba et al. (2010)
			Ellagic acid	Parasite growth	Clin isol	0.07	8	
			Lupeol	Parasite growth	Clin isol	8.3	714	
Physalis angulata L. (Synonym: *Physalis capsicifolia* Dunal)	Solanaceae	Whole plant	Physalin B	pLDH	3D7	0.86	3.63	Mangwala Kimpende et al. (2013)
			5β,6β-epoxyphysalin B	pLDH	3D7	0.62	2.25	
Strychnos icaja Baill.	Loganiaceae	Root	Strychnogucine A	^{3}H-hypoxanthine	FCA	2.310	–	Frédérich et al. (2001)
			Strychnogucine B	^{3}H-hypoxanthine	FCA	0.617	25.12	
			Sungucine	^{3}H-hypoxanthine	FCA	7.816	0.8	
			Isosungucine	^{3}H-hypoxanthine	FCA	1.315	7.0	
			18-hydroxyisosungucine	^{3}H-hypoxanthine	FCA	0.847	19.83	
			Strychnogucine A	^{3}H-hypoxanthine	W2	–	–	
			Strychnogucine B	^{3}H-hypoxanthine	W2	0.085	182.4	
			Sungucine	^{3}H-hypoxanthine	W2	10.14	0.6	
			Isosungucine	^{3}H-hypoxanthine	W2	0.265	34.7	
			18-hydroxyisosungucine	^{3}H-hypoxanthine	W2	0.140	120	
			Strychnogucine A	^{3}H-hypoxanthine	F32	4.813	–	
			Strychnogucine B	^{3}H-hypoxanthine	F32	0.510	–	
			18-hydroxyisosungucine	^{3}H-hypoxanthine	F32	1.263	–	
			Strychnogucine A	^{3}H-hypoxanthine	PFB	3.199	–	
			Strychnogucine B	^{3}H-hypoxanthine	PFB	0.202	–	
			18-hydroxyisosungucine	^{3}H-hypoxanthine	PFB	0.431	–	

SI = selective index.
Clin isol = clinical isolate.

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Afterwards, several cryptolepine analogs (e.g. 2,7-dibromocryptolepine, 1,2-dichlorocryptolepine, 7-bromo-2-chlorocryptolepine, 7-bromo-2-fluorocryptolepine) with high antiplasmodial activity have been synthesized (Wright et al., 2001; Onyeibor et al., 2005).

In continuity with the aforementioned studies, a cryptolepine isomer named neocryptolepine, and a dimeric indoloquinoline alkaloid named biscryptolepine were isolated from *C. sanguinolenta* (Cimanga et al., 1998). These compounds showed interesting antiplasmodial activity against the chloroquine-resistant *P. falciparum* strain K1 (IC_{50} of 2.61 μM and 0.27 μM, respectively) (van Miert et al., 2004, 2005). Furthermore, a series of neocryptolepine derivatives was obtained by organic synthesis (Jonckers et al., 2002). Some of them, such as 2-bromoneocryptolepine and isoneocryptolepine, showed higher antiplasmodial activity than neocryptolepine (van Miert et al., 2004, 2005).

To support the use of *E. villosum* root bark in traditional Congolese medicine to fight malaria, Longanga Otshudi et al. (2005) investigated its methanolic extract. Four biologically active bisbenzylisoquinoline alkaloids were isolated namely cycleanine, cycleanine N-oxide, isochondodendrine and cocsoline. These compounds were evaluated for their potential to inhibit *in vitro* the growth of *P. falciparum* (FcB1-Colombia, chloroquine-resistant strain) and showed high antiplasmodial activity with IC_{50} values ranging from 0.1 to 8.6 μg/ml (Table 3), in agreement with previous results (Frappier et al., 1996; Angerhofer et al., 1999). In another study, the biologically guided fractionation of the alkaloidal extract of *Albertisia villosa* root bark also led to the isolation and identification of three known bisbenzylisoquinoline alkaloids (cycleanine, cocsoline and N-desmethylcycleanine) (Lohombo-Ekomba et al., 2004). Hence, the presence of these alkaloids may support the use of the decoction of the root bark of *A. villosa* in traditional medicine to treat malaria.

From the roots of a Congolese *S. icaja*, Kambu et al. (1980) previously isolated methylstrychnine, three tertiary monomers (icajine; 19, 20-R-epoxynovacine; and 19, 20-R-epoxy-15-hydroxynovacine), and two tertiary dimers (bisnordihydrotoxiferine and a new compound, sungucine). Sungucine exhibited pronounced antiplasmodial activity (IC_{50}=2.3–7.8 μg/ml on FCA 20 strain and 1.66–10.14 μg/ml on W2 strain) while icajine was inactive against the same parasites (Frederich et al., 1999, 2001).

In continuation of their work on Congolese *S. icaja*, Frederich et al. (2000) isolated three new sungucine derivatives, named isosungucine, 18-hydroxysungucine, and 18-hydroxyisosungucine. These compounds, particularly 18 hydroxyisosungucine, were moderately active against *P. falciparum* strains. In a further phytochemical reinvestigation, the authors isolated two new tertiary quasi-symmetric bisindole alkaloids (strychnogucines A and B). Strychnogucine B was highly active *in vitro* and strychnogucine A moderately active against four strains of *P. falciparum* (W2, PFB, F32 and FCA 20) (Table 3). Strychnogucine B was more active against the chloroquine-resistant strains (W2 and PFB) than against the chloroquine-sensitive ones (F32 and FCA 20) (Frederich et al., 2001).

Bringmann et al. screened four *Ancistrocladus* species collected in four different areas of the Province Orientale (Bringmann et al., 2000, 2002, 2003, 2006, 2008). In their phytochemical and biological investigation, the authors performed the isolation and structural elucidation of new naphthyisoquinoline alkaloids as well as their antiplasmodial evaluation. Ancistroealaines A and B were isolated from the extracts of roots of *Ancistrocladus ealaensis* and possessed IC_{50} values ranging between 0.52 and 4.0 μg/ml on *P. falciparum* K1 and NF54 strains (Bringmann et al., 2000).

In a subsequent study, ancistrocongolines A–D along with the known alkaloid korupensamine A were isolated from *Ancistrocladus congolensis* (Bringmann et al., 2002). All the compounds exhibited antiplasmodial activities with IC_{50} values lower than 3 μg/ml (Table 3). Ancistrolikokine D, a new naphthylisoquinoline was isolated from the roots of *Ancistrocladus likoko* in addition to ancistrolikokine A–C, ancistroealaine A and korupensamine A. The new compound exhibited interesting antiplasmodial activity against the strains K1 (IC_{50}=0.79 μg/ml) and NF54 (IC_{50}=1.16 μg/ml) of *P. falciparum* (Bringmann et al., 2003).

From the roots of *Ancistrocladus* taxon, with close affinities to *A. congolensis*, Bringmann et al. (2008) isolated six new naphthylisoquinoline alkaloids: 5'-0-demethylhamatine, 5'-0-demethylhamatinine, 6-0-demethylancistroealaine A, 6,5'-0,0-didemethylancistroealaine A, 5-epi-6-0-methylancistrobertsonine A and 5-epi-4'-0-demethylancistrobertsonine C. The IC_{50} values of all these compounds were lower than 3 μg/ml (Table 3).

In another study, these authors also reported the isolation and structure elucidation of three N,C-coupled naphthyldihydroisoquinolinium namely ancistrocladinium A and ancistrocladinium B (with its atropisomer). These compounds isolated from a Congolese *Ancistrocladus* species represent a novel-type subfamily of the naphthylisoquinoline alkaloids and showed an antiplasmodial activity with IC_{50} lower than 1 μg/ml (Bringmann et al., 2006).

From the 80% ethanol extract of *N. pobeguinii*, five known compounds were isolated and identified: strictosamide (**1**), (5S)-5-carboxystrictosidine (**2**), 19-0-methylangustoline (**3**), 3-0-β-fucosyl-quinovic acid (**4**) and 3-ketoquinovic acid (**5**) (Mesia et al., 2010a; Xu et al., 2012). Compound **1**, the major alkaloid of the crude extract (IC_{50} > 64 μM on K1 strain) may act as a prodrug as reported previously (Camacho et al., 2004; He et al., 2005). However, in another study, this compound was reported to exhibit pronounced antiplasmodial activity against the K1 (chloroquine and pyrimethamine-resistant) and NF54 (chloroquine-sensitive) strains of *P. falciparum* with IC_{50} of 0.45 μg/ml and 0.37 μg/ml, respectively (Abreu and Pereira, 2001). Compounds **2** and **3** were isolated for the first time from *N. pobeguinii*, but the authors did not exclude the fact that compound **3** might be an artefact formed during extraction and isolation using methanol. Compound **2**, **3** and **4** exhibited antiplasmodial activity with IC_{50} values of 41.2 μM, 26.5 μM and > 64 μM, respectively.

In the paper by Musuamba et al. (2010), three known compounds (lupeol, quercetin and ellagic acid) were isolated from *Phyllantus amarus* apical stem and bioassayed for their antiplasmodial activity against a Congolese chloroquine-sensitive strain of *P. falciparum*. Results from this testing indicated that quercetin exhibited IC_{50} values of 3.2 μg/ml, in agreement with previous study (Cimanga et al., 2009). In addition, ellagic acid displayed pronounced *in vitro* antiplasmodial activity (IC_{50} < 0.1 μg/ml) that was higher than that of lupeol (IC_{50}=8.3 μg/ml).

Physalin B and a mixture of physaline B and 5β,6β-epoxyphysalin B were isolated from a Congolese *P. angulata* (Mangwala Kimpende et al., 2013). The *in vitro* antiplasmodial activity of physaline B and of the mixed crystal containing the two physalin B-like molecules against the 3D7 (chloroquine-sensitive) strain of *P. falciparum* showed IC_{50} values of less than 1 μg/ml (Table 3).

Yadanziolide A, yadanzioside C and yadanzioside F isolated from the ethyl acetate extract of *B. sumatrana* seeds exhibited pronounced antiplasmodial activity against a Congolese chloroquine-sensitive strain of *P. falciparum* with IC_{50} values of 0.02 μg/ml, 5.60 μg/ml and 3.50 μg/ml, respectively (Penge et al., 2013).

Among parasitemias, *P. falciparum* is the most prevalent species in the DR Congo (90.4%). *Plasmodium malariae* is present in 8.7% of parasitemias while *Plasmodium ovale* parasitemia is rare (< 1%) (Taylor et al., 2011). *P. falciparum* is present either as monoinfection or as coinfection with *Plasmodium malariae* or *P. ovale*, or all three species. Even if the prevalence of *P. ovale* is low in the DR Congo, this parasite forms hypnozoites (i.e. parasite stages in the liver) which can lead to multiple relapses after the primary infection. Hence, the antiplasmodial sensitivity of extracts, fractions and isolated compounds would be also screened against the blood stages of both

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Plasmodium malariae and *P. ovale*. In addition, the ability of the different plant-derived products to cure the liver stage infections should also be evaluated by the type II FAS-target-based antimalarial screening approach (Tasdemir et al., 2005; Tasdemir, 2006) or the real time measurements of bioluminescence of *in vitro* cultured liver stages (Ploemen et al., 2009). Finally, to check a possible disparity in parasite drug sensitivity, the *ex vivo* susceptibility of *P. falciparum* to plant extracts would also be evaluated against clinical isolates collected from regions where the herbal preparation is mainly used traditionally to treat malaria or malaria-like symptoms.

2.3. *In vitro* cytotoxicity of extracts, fractions and isolated compounds

Besides their antiplasmodial activity, the cytotoxicity of plant-derived products on human cells is also of interest. For this purpose, the cytotoxicity evaluation of these plant-derived products was performed. Briefly, cell lines MRC-5 (human lung fibroblast), WI-38 (human normal fetal lung fibroblast), L6 (rat skeletal muscle), KB (human epidermoid carcinoma) or J774 (murine macrophage-like cells) were incubated on a 96-well tissue culture plate with the natural products for 48 h (or more). After this period of incubation, cell viability was assessed using the tetrazolium salt (MTT, WST-1 or NBT) colorimetric method based on the cleavage of the reagent to formazan dye by mitochondrial dehydrogenase in viable cells (Mosmann, 1983). The absorbance was measured at 450 nm (or 540–560 nm) with a scanning multiwell spectrophotometer and the percentage of cytotoxicity calculated (Kuypers et al., 2006; Stevigny et al., 2002).

To evaluate the selective activity of the extracts or isolated compounds against the *P. falciparum* parasite compared to its cytotoxicity for mammalian cells, their selectivity index has been determined. The selectivity index (SI) was defined as the ratio of the cytotoxic CC_{50} value on a cell line to the antiparasitic IC_{50} value on a *P. falciparum* strain.

In considering the publication of Camacho et al. (2003), a SI greater than 1 suggests that the extracts or fractions are selective against the *Plasmodium* parasite, i.e., they are at least one-fold more active against the parasite than against the mammalian cell line. By contrast, extracts or fractions with $SI < 1$ are considered to be selective against the cell line used. Plant-based antimalarial agents with promising selectivity indexes ($SI > 1$) warrants further investigations. Interestingly, most of the investigated extracts and fractions from Congolese medicinal plants possessed a $SI > 1$, that is, only few plant species such as *E. chlorantha* was devoid of selective action with $SI < 1$ (see Table 1). However, it must be noted that SI values for lead compounds should be higher than 10 or even 100 (Pink et al., 2005; Rasoanaivo et al., 2004).

An additional *in vitro* erythrocyte toxicity study was recently introduced to check the hemolytic potential of extracts or compounds (Rasonaivo et al., 2004; Memvanga et al., 2013a). Negligible red blood cells lysis activity ($< 5\%$) suggests that the observed antiplasmodial activity is not a result of a hemolytic effect, but a real action of the extract or compound against the parasite.

Yet it is important to keep in mind that *in vitro* cytotoxicity and hemolytic toxicity do not always correlate with *in vivo* observations. Indeed, they are not always a clear indication of cytotoxicity *in vivo* because of the selectivity index value depends strongly on the cell line and plasmodial strain tested (Lumpu et al., 2013; Kikueta et al., 2013; Frederich et al., 2001). In addition, test samples are incubated with mammalian cells for 48–72 h (or up to 7 days) which are unlikely to happen *in vivo* taking into account the half-life or circulating time in blood stream of many compounds. Therefore, in order to confirm the safety of plant extracts after oral administration, various *in vivo* toxicity studies including acute and subacute oral toxicity should also be conducted.

3. *In vivo* antimalarial activity and toxicity of plant-derived products

3.1. *In vivo* antimalarial activity

The search for efficient and less toxic antimalarials that are effective against multidrug resistant *Plasmodium* species constitutes one of the main strategies in combating malaria. As mentioned above, quite a large number of extracts, fractions and molecules from Congolese plants with significant antiplasmodial activity *in vitro* have been identified and constitute promising candidates in malaria therapy. However, an *in vitro* effective antiplasmodial extract should also have strong *in vivo* antimalarial activity. Therefore, *in vivo* investigations must be performed to correlate with *in vitro* data.

For this purpose, some crude extracts from Congolese medicinal plants were assessed for *in vivo* activity against *Plasmodium berghei*, *P. berghei* ANKA or *Plasmodium yoelli* N67 infection in mice. The schizontocidal activity of the natural products was evaluated in early infection (suppressive 4-day Peter's test) (Knight and Peters, 1980), unless otherwise specified. Antimalarial efficacy was then assessed by the assessment of the parasitemia level, the activity, the mean survival time and the survival rate of mice for up to 14–28 days following inoculation. Chloroquine or quinine was used as antimalarial reference product. The chemosuppression was determined as follow: $\%\ \text{suppression} = [(A-B)/A] \times 100$ where A is the mean parasitemia in the negative control group and B the mean parasitemia in the test group (Tona et al., 2001). In the following lines, we highlight the *in vivo* studies performed with Congolese antimalarial plants.

In one of the first *in vivo* antimalarial screening, Tona et al. (1999) evaluated the ability of *E. hirta* whole plant and *C. sanguinolenta* root bark to reduce parasitemia in *P. berghei*-infected mice. They reported that the suppression of parasitemia produced by their ethanolic and dichloromethane extracts (200 mg/kg, oral) was ranged between 63.0% and 70.0%, in agreement with previous results (Cimanga et al., 1997b). In addition, at a daily oral dose of 50 mg/kg, cryptolepine and its hydrochloride isolated from *C. sanguinolenta* root bark exhibited a significant chemosuppression of parasitemia (80–90%) in mice infected with *P. yoelli* N67 (Cimanga et al., 1997b).

Administered orally at 200 mg/kg in *P. berghei*-infected mice, the ethanolic and aqueous extracts of *M. morindoides* leaves showed antimalarial activity of 22.6% and 31.3%, respectively. By contrast, the dichloromethane extract of *M. morindoides* leaves produced 74.0% chemosuppression after oral administration (Tona et al. 2001). Surprisingly, this parasitemia suppression dropped to 33.0% when the leaves were collected in August (dry season) (Tona et al., 1999) instead of in March (rainy season) (Tona et al., 2001). These results suggest that the concentration of the active constituents may be influenced by the timing of plant collection. Additionally, when tested at an oral dose of 200 mg/kg, the ethanolic and dichloromethane extracts of *C. occidentalis* root bark and *Phyllanthus niruri* whole plant reduced parasitemia by 60–75%. However, the aqueous extract of these two plant parts were less active than the corresponding ethanolic and dichloromethane extracts (Tona et al., 2001).

Different extracts from the leaves of *M. morindoides* collected in rainy season were assessed for their antimalarial activity in mice infected with *P. berghei*. Administered at oral doses ranging from 200 to 800 mg/kg, the 80% methanol showed higher activity extract (54.2–59.7% chemosuppression) than that of the aqueous (22.5–38.0% chemosuppression) and ethanol (33.3–38.7% chemosuppression) extracts. The most active samples were the dichloromethane extract and the petroleum ether soluble fraction from the partition of the ethanol extract (73.2–82.9% chemosuppression) (Cimanga et al., 2009).

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At a daily oral dose of 200 mg/kg, the dichloromethane extract of the stem bark of *C. mubango*, the stem bark of *N. pobeguinii* and the leaves of *P. staudtii* produced, respectively, 92.3%, 95.4% and 94.4% chemosuppression in *P. berghei*-infected mice. The aqueous extracts of *C. mubango*, and *N. pobeguinii* produced a slightly lower but still significant inhibition of the day-4 parasitemia (60–80%) whereas that of *P. staudtii* only suppressed the parasitemia by 37.0% (Mesia et al., 2005).

The 80% ethanolic extract of *N. pobeguinii* stem bark (300 mg/kg × 5 days; oral) led to a pronounced reduction of parasitemia by 86.0% in *P. berghei*-infected mice, and by 75.0% in *P. yoelli*-infected mice (Mesia et al., 2010a). The mean survival time of the extract- and chloroquine-treated group was 16 days and 18 days, respectively. Prolonging the oral dosing of this extract to 2 × 5 days with an interruption of 2 days led to 92.0% reduction of parasitemia. Recrudescence appeared rapidly in the 5-day dosing and more slowly in the 2 × 5 days dosing.

During *in vivo* studies conducted by Cimanga et al. (2006b), the ethanolic, dichloromethane and petroleum ether extracts of *M. lucida* leaves (200 mg/kg, oral) produced, respectively, 62.5%, 67.5% and 76.2% of chemosuppression of parasitemia in mice infected with *P. berghei*. Additionally, for the first time, the antimalarial activity of oleanolic acid and ursolic acid isolated from *M. lucida* was assessed. The chemosuppression of oleanolic acid (200 mg/kg, oral) was determined at 37.4% while ursolic acid (200 mg/kg, oral) produced even greater reduction in parasitemia of 97.7%, as previously reported (Amusan et al., 1996).

In *P. berghei*-infected mice, both ethanol extracts from *P. amarus* whole plant and 3-month-old callus extracts from *P. amarus* fresh apical stems led to chemosuppression of 79.3% and 77.3%, respectively (Musuamba et al., 2010).

The *in vivo* antimalarial activity of aqueous extracts of *P. angulata* leaves, *A. chinensis* whole plant and *E. palustre* stem bark was also evaluated (Lusakibanza et al., 2010). In mice infected with *P. berghei*, *A. chinensis* (300 mg/kg, oral) caused a very significant inhibition of parasite growth (85.6%) while *P. angulata* and *E. palustre* (300 mg/kg, oral) showed good antimalarial activity (58.7% and 52.1% chemosuppression, respectively). In this study, the oral therapy started at day-5 post-inoculation (curative test). Therefore, we can speculate that start of treatment in the very early stage of the disease may reduce mortality by favoring quick resolution of symptoms and by preventing hyperparasitemia (Memvanga and Préat, 2012; Memvanga et al., 2013a). Additionally, since its aqueous extract was inactive *in vitro* ($IC_{50} > 100$ μg/ml), the *in vivo* activity of *E. palustre* may be the result of a metabolical activation of certain plant constituents in the gastrointestinal tract.

The antimalarial activity of *V. amygdalina* leaves has also been evaluated *in vivo* by Ngbolua et al. (2011a). Administered in *P. yoelli*-infected mice (500 mg/kg, oral), the ethanolic extract of this plant part led to 62.3% chemosuppression of parasitemia.

At oral dose of 50–200 mg/kg, the aqueous, ethanol and ethyl acetate extracts of *B. sumatrana* seeds produced 60.3–68.2%, 66.1–72.7% and 71.5–76.4% chemosuppression of parasitemia in mice infected with *P. berghei* ANKA, respectively (Penge et al., 2013).

As summarized in Table 3, several compounds were isolated from Congolese antimalarial plants. *In vitro*, some of them exhibited IC_{50} values lower than their source crude extracts. It is the case of yadanziolide A (from *B. sumatrana*), ursolic acid (from *M. lucida*), ellagic acid (from *P. amarus*), physalin B (from *P. angulata*), quindoline, hydroxycryptolepine, cryptolepine and cryptolepine hydrochloride (from *C. sanguinolenta*). However, the evidence that these compounds have higher *in vitro* and/or *in vivo* antimalarial activity than their source extracts cannot be produce because comparable concentrations or equivalent doses of active compounds and extracts were not tested in the different experiments. For example, the ethanolic extract and ursolic acid from *M. lucida* were evaluated in mice at the same oral dose of 200 mg/kg (Cimanga et al., 2006b). Obviously, further complementary *in vitro* and preclinical studies with more appropriate study design are needed in this field. Additionally, these preclinical studies should also evaluated the rapidity of onset of antimalarial activity, the time to onset of recrudescence and the prolonging of the mean survival time as well as the effectiveness of different plant-derived products against intrahepatic forms of human malaria parasites.

For many years, the rodent malaria parasites have been recognized as useful model parasite for evaluation of *in vivo* antimalarial efficacy of drugs, in particular for uncomplicated falciparum malaria (Killick-Kendrick and Peters, 1978). Unfortunately, some *in vivo* studies performed in murine malaria model were disappointing, regardless the timing and locations of plant material (re)collection, the life cycle stage of the tested parasite *in vitro* and the method of preparation of extracts (e.g. decoction instead of maceration).

Several hypotheses can address these observations. First, some extracts or compounds might alter the properties of host erythrocytes required for survival and growth of the parasites in cultures (Chakrabarti et al., 2013) thereby leading to underestimated IC_{50} values. To avoid artefact, the comparative parasite growth patterns of pre-incubated erythrocytes with extracts or compounds and non pre-incubated erythrocytes should be also performed in cultures. Second, the parasitemia difference between the *in vitro* (1–2%) and *in vivo* (2–8% at the first day of the treatment) studies might explain some of these observations. Finally, the low gastrointestinal stability and/or permeability as well as the possible intestinal and hepatic metabolism of some extracts/compounds may influence their oral bioavailability and efficacy.

On the other hand, as indicated above, some extracts that are less active *in vitro* ($IC_{50} > 50$ μg/ml) exhibited interesting antimalarial activity *in vivo* (Mesia et al., 2010a; Lusakibanza et al., 2010). Indeed, some constituents of extracts can become effective *in vivo* after a metabolic activation thereby acting as prodrugs. In addition, some extracts, fractions or constituents that are inactive against the parasite itself may have beneficial effect in the host immune system and/or in the inflammatory process evolving during malaria infection (Memvanga, 2013b; Rasoanaivo et al., 2011). For instance, oleic acid and linoleic acid (IC_{50} = 18–27 μg/ml on 3D7 strain) extracted from *A. chinensis* (Lusakibanza, 2012) may have immunomodulator properties, as previously reported (Memvanga and Préat, 2012; Memvanga et al., 2013a; Kumaratilake et al., 1997; Kinsella et al., 1990; Fritsche, 2006). In addition, oleic acid might inhibit the endothelial overexpression of the vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin during malaria infection. Oleic and linoleic acids might also reduce interferon and interleukin-2 production (Carrillo et al., 2012a, 2012b) thereby avoiding progressive immune pathologies and severe forms of malaria.

3.2. *In vivo* toxicity

The adverse effect profile and tolerability of antimalarial drugs are of important considerations. Therefore, acute and sub-acute toxicological studies were also performed during preclinical studies. During toxicological evaluations, any signs of toxicity, mortality, or changes in body weight were observed. Before sacrificing the animals, blood samples were also collected for hematology. The biochemical parameters (serum glutamate-oxaloacetate transaminase and serum glutamate-pyruvate transaminase) were used to evaluate the hepatic toxicity associated with the crude extracts in mice. Their potential nephrotoxicity was also determined in the serum samples by estimating serum creatinine and urea levels. These results were further supported by histopathological analysis of the vital organs (liver, kidney, brain, heart, lung, large intestine). The 50% lethal dose (LD_{50}) of crude extracts from a single administration was also determined.

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Only few toxicological evaluations on Congolese plants have been performed according to the literature. These are *N. pobeguinii*, *C. mubango*,, *P. staudtii* (Mesia et al., 2005), *C. occidentalis*, *Phyllantus niruri* (Tona et al., 2001), *M. morindoides* (Tona et al., 2001; Cimanga et al., 2009), *Nauclea latifolia* (Mesia et al., 2010a), *A. chinensis*, *P. angulata* (Lusakibanza, 2012), *A. congensis* (Nsaka et al., 2013) and *D. sarmentosa* (Jobalo, 2013). In general, no toxic effect or mortality was observed in mice treated at the administered dose for all the plant aqueous extracts. Moreover, during histopathological examinations, no significant macroscopic or microscopic lesions were observed in the vital organs of any mouse. For the majority of tested extracts, their LD_{50} was estimated to be greater than 5000 mg/kg body weight thereby suggesting their safety for human use (Kennedy et al., 1986).

Yet, oral administration of aqueous extracts from *C. mubango* stem bark and *N. pobeguinii* stem bark constitute the two only exceptions of relative toxicity observed in mice (Mesia et al., 2005). Indeed, in the sub-acute toxicity tests, the *N. pobeguinii* aqueous extract (5000 mg/kg) slightly increased the serum concentration of glutamate-oxaloacetate transaminase while the aqueous extract of *C. mubango* (250 mg/kg) significantly increased the serum concentrations of both glutamate-oxaloacetate transaminase and glutamate-pyruvate transaminase. In addition, at doses higher than 250 mg/kg, the oral dosing of *C. mubango* aqueous extract resulted in some adverse effects, such as diarrhea, asthenia and palpitations.

As shown above, to evaluate acute or chronic nephrotoxicity, clinical markers of kidney injury and histopathological analyses were performed during the different *in vivo* toxicity assessment. However, it is important to keep in mind that the ability of the kidneys to compensate renal mass loss and to recover after acute insult as well as the lack of specificity of the measured markers (creatinine and urea) constitute the main limitations of these testing methods (Ouedraogo et al., 2012). Therefore, to better investigate the nephrotoxicity potency of herbal medicines, others biomarkers (e.g. calbindin, clusterin, osteopontin, VEGF, etc.) that are more specific and more sensitive should also be measured (Hoffmann et al., 2010). Additional *in vitro* and *in vivo* methods for genotoxicity and teratogenicity assessment should also be performed (see Ouedraogo et al., 2012 for review).

Finally, to obtain complementary data confirming the safety of Congolese antimalarial plants, the *in vitro* and *in vivo* studies should not be limited to the evaluation of their cyto- and organotoxicity. The potential of these plants to modulate the effect of P-glycoprotein or to interact with one or more cytochrome P450 enzymes would be investigated by using *in vitro* intestinal cell models (Caco-2 cells, HT29-MTX cells, etc.) (Memvanga and Préat, 2012; Memvanga et al., 2013a, 2013c; Hou et al., 2007, 2008). In addition, during *in vivo* studies, possible herb-drug (or herb-herb) interactions would also be assessed. Indeed, a pharmacokinetic interaction between the aqueous extract of *G. kola* seeds and ciprofloxacin (Esimone et al., 2002), and an inhibition of drug metabolizing enzymes (cytochrome P450s) by the methanol and aqueous extracts of *P. amarus* whole plant (Appiah-Opong et al., 2008; Hari Kumar and Kuttan, 2006) were reported.

4. Clinical studies and commercialized plant-derived products

To evaluate the tolerability, safety and efficacy of phytotherapeutic products in humans, clinical trials should be conducted for (uncomplicated) malaria. However, in the DR Congo, few data from these clinical studies is available in the literature. The limited funding and financial support may explain the few studies in this field.

To assess its proof of concept, a quantified 80% ethanol extract from the stem bark of *N. pobeguinii* (PR 259 CT1) containing 5.6% strictosamide was submitted to clinical Phases I, IIA and IIB studies in Kinshasa (DR Congo) (Mesia et al., 2010b, 2012a, 2012b). The strictosamine content of this standardized *N. pobeguinii* preparation was guaranteed by the development and validation of an HPLC-UV method (Dhooghe et al., 2008).

During the Phase I clinical trial, 15 male volunteers (50–70 kg, 18–40 years) were treated in an outpatient clinic with a drug regimen of two 500 mg capsules three times daily for seven days, during meals. The oral administration of this plant extract induced no significant changes in the concentration levels of all investigated hematological, biochemical, electrocardiogram and vital sign parameters as well as physical characteristics compared to those seen in the baseline data. The concentration levels of all evaluated parameters were within the normal limits as reported in the literature. All adverse events noted were mild and self-resolving including increase of appetite (33%), headache (20%) and nausea (20%). Other minor side effects were insomnia, somnolence and asthenia (7%) (Mesia et al., 2010b).

Based on these encouraging results, a phase IIA clinical trial was designed to continue safety assessments and evaluate the efficacy of this quantified extract in 6 men and 5 women (61.1 kg, 25.7 years on average) diagnosed with uncomplicated *falciparum* malaria (Mesia et al., 2012a). This phase IIA study was an open cohort study carried out according to the WHO 2003 guidelines for 14-day test. The herbal medicinal product was administered with a dose regimen of two 500 mg capsules three times daily for three days, followed by outpatient treatment of one 500 mg capsule three times daily for the next four days. The results revealed that 10 patients were completely cleared of parasitemia and fever on days 3, 7, and 14 while one patient experienced a recurrence of parasitemia at days 7 until 14. This trial also reported that the quantified extract was well tolerated with only mild and self-resolving adverse effects including fatigue and headache, in agreement with those found in the phase I clinical trial (Mesia et al., 2010b). Interestingly, all symptoms progressively disappeared, and no symptoms were observed on day 14.

According to the promising results obtained during phase I and phase IIA clinical trials (Mesia et al., 2010b, 2012a), a Phase IIB study was also conducted as a single blind prospective trial in 65 patients with proven *falciparum* malaria to evaluate the effectiveness and safety of the aforementioned herbal drug (Mesia et al., 2012b). Patients were treated with a drug regimen of two 500 mg capsules three times daily for three days in the inpatient clinic, followed by out-patient treatment of one 500 mg capsule three times daily during the next four days. The study was carried out simultaneously using a fixed-dose of artesunate (100 mg) and amodiaquine (270 mg) as a positive control. The positive control group received two tablets once daily during three consecutive days. Antimalarial responses were evaluated according to the WHO 2003 guidelines for a 14-day test. The results from the physical and laboratory examinations did not show any significant changes in values of vital signs, electrocardiogram, biochemical, and hematological parameters. The study showed a significant decreased parasitaemia in patients treated with the quantified extract and artesunate-amodiaquine with adequate clinical parasitological responses at day 14 of 87.9% and 96.9%, respectively. With fewer side effects, the quantified extract was better tolerated than the artesunate–amodiaquine combination.

Finally, based on the adequate clinical and parasitological response during these three clinical trials, the herbal medicinal product consisting of an 80% ethanolic extract of the stem bark of *N. pobeguinii* containing 5.6% strictosamide can be considered as a promising candidate for the development of an herbal medicine for the treatment of uncomplicated *falciparum* malaria. However, it must be noted that the aforesaid clinical trials did not cover non-immune patients (e.g. children) which are considerably more affected by the malaria infection. Therefore, much more clinical research is needed in this field.

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In 2013, 54 patient volunteers suffering from malaria were treated during 10 days with capsules containing powdered leaves of *A. annua* from Katanga (DR Congo). All patients were free of fever after two days and 51 were free of parasites after 10 days. Thereafter, a second trial carried out during 7 days with 82 patient volunteers confirmed the results obtained previously (Weathers et al., 2014). Previously, 53 patients with fever and parasitaemia (47 *P. falciparum*, 6 *Plasmodium malariae*) were treated daily with 5 g of *A. annua* tea (0.58% of artemisinin content) for 4 days during two different trials. On the last day of the treatment, more than 90% of the patients were free of trophozoites and about 80% free of malaria symptoms. Approximately 25% of patients complained about nausea during the treatment, which disappeared when the treatment course finished. No other side effects were observed (Mueller et al., 2000). These results are encouraging; however, the therapeutic efficacy of *A. annua* tea to treat human malaria is still a matter of debate due to its short-term protection (high rate of recrudescence) and possible development of malaria parasites resistant to artemisinin (WHO, 2012). Therefore, to overcome these drawbacks, a combinatorial approach using *A. annua* and *Curcuma longa* extracts has been proposed (Mimche et al., 2011, Rasoanaivo et al., 2011; Memvanga et al., 2013a).

Additionally, it is noteworthy that *Cinchona succirubra*, *Cinchona calisaya* and *Cinchona ledgeriana* cultivated in the DR Congo led to the isolation of quinine. Tablets, sirups, drops and injections containing this alkaloid are prepared by Pharmakina®, a Congolese pharmaceutical industry and commercialized in many African countries. Two others phytomedicines that contain extracts of either *G. kola* (Nsansiphos®) or *C. occidentalis and N. latifolia* (Manalaria®) are government approved and belong to the Congolese List of Essential Drugs (LNME, 2010). Another Congolese phytomedicine containing a mixture of extracts from *L. camara*, *Gardenia ternifolia* and *Crossopteryx febrifuga* (Kabala et al., 2005) is under registration.

As this review has shown, the wealth of *in vitro* and preclinical data has provided a strong basis for the potential of several Congolese medicinal plants as antimalarial agents. Interestingly, some of these data progress to the trialing of various plants in human subjects. However, dose-escalation studies in human volunteers suffering from uncomplicated malaria should be undertaken. Thereafter, the minimal clinically effective dose can be selected for further clinical assessments of these promising phytomedicines. Such studies should include larger numbers of patients so as to generate clinical data on safety and efficacy of the potential new antimalarial agents. Randomized comparative (artemether-lumefantrine) controlled double- blind design should be adopted for the phase III clinical trials.

Additionally, the development of validated analytical methods for the identification and quantification of traditional Congolese herbal medicines constitute a prerequisite to better characterize them and evaluate their efficacy during clinical studies. Indeed, these methods may contribute to the evaluation of the quality of such herbal medicines as well as the preparation of standardized extracts. For this purpose, the HPLC-UV methods for the quantification of the main constituent and putative active principle of *G. kola* (Tshisekedi et al., 2014) and *P. amarus* (Dhooghe et al., 2011) extracts were developed.

5. Conclusion and perspectives

The use of traditional medicinal plants remains entrenched in the healing practices of Congolese population. Currently, plant-based products represent a progressive trend in the primary healthcare system of the DR Congo, in line with the objectives of the "Traditional Medicine Strategy" proposed by the World Health Organization (WHO, 2013b).

With proven research methods, the potential of many Congolese medicinal plants to yield new antimalarial drugs has been confirmed both *in vitro* and *in vivo*, as reviewed here. The majority of studies presented in this review were focused on determining the antiplasmodial activity of plant extracts. This methodology approach is of interest since some crude extract can be more active than their fractions or isolated compounds, as a result of (i) additive or synergistic effects between different plant constituents, (ii) immunomodulatory, anti-inflammatory and/or antipyretic properties, (iii) pharmacokinetic and pharmacodynamic interactions as well as (iv) capacity to counteract adverse effects (Rasoanaivo et al., 2011). However, over the next years, consideration should be given first to the extracts obtained according to the traditional preparation methods, and then to the extracts prepared with solvents other than those used in the traditional remedies.

Roots constitute approximately a quarter of the studied plant materials. However, taking into account the destructive harvesting nature of root plant materials, the further investigations should be focused on active leaf plant materials. In addition, different kind of studies should be kept up in order to uncover better knowledge relating to taxonomy, ethnobotanic, reproductive biology (seed germination and tissue culture), geographical and seasonal variation as well as horticulture of antimalarial plants from the DR Congo.

Moreover, given that more than 200 medicinal plants traditionally used in the management of malaria in the DR Congo were identified during different ethnopharmacological studies, it would also be interesting to bioassay Congolese traditional plant-based remedies that have not yet been validated scientifically. Future research design should also investigate the combinatorial effect of different Congolese antimalarial plants as well as their potential in the prophylaxis of malaria. More attention also needs to be directed towards the assessment of other beneficial properties of these plants in malaria management (e.g. antioxidant activity).

The development of more effective, affordable and standardized phytopharmaceutical drugs in close collaboration with galenists, analysts, clinicians and industrials would also be worthwhile. To this end, extracts from the seeds of *B. sumatrana* and those from the leaves of *T. gilletii*, *A. congensis*, *M. lucida*, *A. cordifolia* and *C. occidentalis* may constitute interesting samples for development of herbal preparations. Therefore, quality of herbal substance applied from the Good Manufacturing Practice or Good Agricultural and Collection Practice should be followed. More pharmacological (e.g. herb–drug or herb–herb interactions and pharmacokinetic parameters) and toxicological (e.g. genotoxicity and teratogenicity) studies should be pursued in order to better validate the safety of these different plant-derived substances. Pharmacovigilance of traditional herbal medicinal product will be also essential for the monitoring of their safety by detecting unwanted reactions, difference in pharmacogenomics and metabolization, etc. Finally, to ensure future success in the research and development of traditional herbal medicines for malaria, laws and regulations regarding the use, marketing and registration of manufactured herbal medicines should be enacted and/or strengthened.

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