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Review

Potential antimalarials from Nigerian plants: A review

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ABSTRACT

Malaria, caused by parasites of the genus *Plasmodium*, is one of the leading infectious diseases in many tropical regions, including Nigeria, a West African country where transmission occurs all year round. Many of the inhabitants use plants as remedies against fever and other symptoms of acute malaria, as reported herein. Some of these plants have their antimalarial efficacies scientifically demonstrated and the active compounds isolated with their probable mechanisms of action studied. Medicinal plants are used to treat diseases also where the biodiversity of plants occur in parallel with endemic transmission of malaria. This review focuses on medicinal plants which are used to treat malaria in Nigeria, and on antimalarial testing of extracts and purified compounds from plants. Some show intense activity against malaria parasites *in vitro* and in experimentally infected mice. The search for new drugs based on plants is important due to the emergence and widespread of chloroquine-resistant and multiple drug-resistant malaria parasites, which require the development of new antimalarials. An acquaintance with antimalarial plants may be a springboard for new phytotherapies that could be affordable to treat malaria, especially among the less privileged native people living in endemic areas of the tropics, mostly at risk of this devastating disease.

Contents

1. The malaria burden

Malaria is a parasitic disease transmitted by the bites of *Anopheles* mosquitoes infected with *Plasmodium* species, four of which infect humans: *Plasmodium falciparum* (the most deadly one), *Plasmodium. vivax, Plasmodium malariae* and *Plasmodium ovale*. The disease primarily affects poor populations in tropical and subtropical areas, where the temperature and rainfall are suitable for the development of vectors and parasites (Greenwood et al., 2008). More than 40% of the world population is at risk of the disease (Snow et al., 2005). An estimated 1.2 billion are at high risk of transmission (≥1 case per 1000 population), half of which live in the African regions; 80% of such cases are concentrated in 13 countries, and over half in Nigeria, Congo, Ethiopia, Tanzania and Kenya (WHO, 2008a).

Nigeria accounts for a quarter of all malaria cases in Africa (WHO, 2008a). In the southern part of the country, transmission occurs all year round while in the north it is more seasonal. Almost all malaria cases in the country are caused by *Plasmodium falciparum*, considered to be the leading cause of death worldwide in 2004, from a single infectious agent (WHO, 2008b). Malaria is the most

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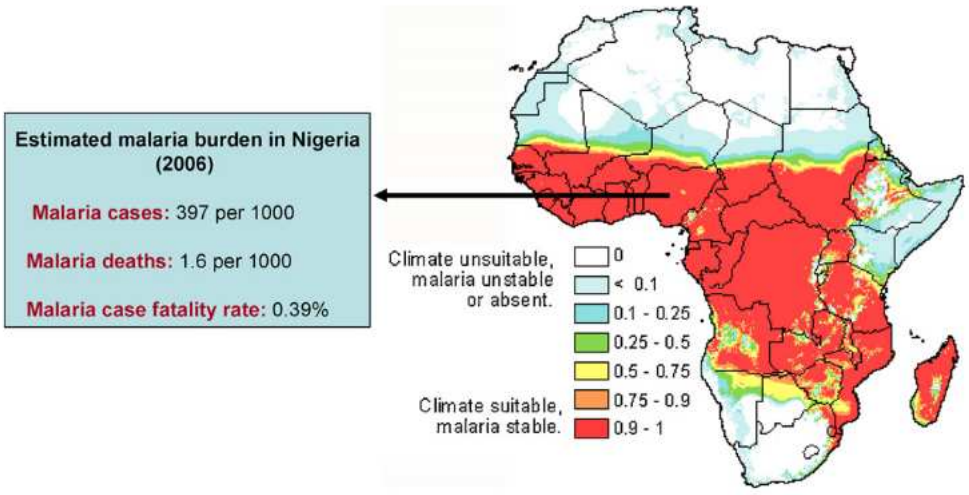

Fig. 1. Human malaria distribution in Africa and its estimated burden in Nigeria. [Adapted from WHO, 2008a, and MARA/AMRA (http://www.mara.org.za)].

common disease in Nigeria; according to the Federal Ministry of Health (2004), half of its population will have one or more malaria attacks annually.

The continuous spread of *Plasmodium falciparum* resistance to antimalarial drugs poses a serious threat to malaria control programs. In Nigeria, a nationwide surveillance data on drug efficacy showed that chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) are no longer viable therapeutic options for the effective treatment of human malaria (Federal Ministry of Health, 2004). Although vaccines could be the best long term control option, they are still undergoing clinical trials (Alonso et al., 2005; Aponte et al., 2007; Bejon et al., 2008; Guinovart et al., 2009). This, in addition to the increased number of drug-resistant parasites, makes the development of novel antimalarials urgent. The high cost of malaria treatment has left the poor masses of Nigeria heavily reliant on traditional practitioners and medicinal plants for the treatment of the disease.

2. Medicinal plants for malaria treatment

Traditional herbal medicines have been used to treat malaria for thousands of years in various parts of the world. The first antimalarial drug used in the Occident was extracted from the bark of the *Cinchona* (Rubiaceae) species, the alkaloid quinine, still largely used. Infusions of the plant bark were used to treat human malaria as early as 1632 (Baird et al., 1996). Years later quinine was isolated and characterized (Saxena et al., 2003), thus becoming the oldest and most important antimalarial drug. Another ancient medicinal plant of millenium use in the West is *Artemisia annua*, rediscovered in China in the seventies as an important source of the antimalarial artemisinin (Bruce-Chwatt, 1982; Klayman, 1985). Artemisinin-combined therapies (ACT) were formally adopted as first-line treatment of uncomplicated malaria in Nigeria from 2005 onwards (Mokuolu et al., 2007). However, ACT use is limited due to its high costs, limited production of artemisinin derivatives to Good Manufacturing Practices (GMP) standards and toxicity (Haynes, 2001; Malomo et al., 2001; Borstnik et al., 2002; Adebayo and Malomo, 2002; Afonso et al., 2006; Boareto et al., 2008).

Neither the Cinchona plants nor *Artemisia annua*, from which the most potent drugs (quinine and artemisinin) were isolated, are indigenous to sub-Saharan Africa. Tropical rainforest plants are known to have higher concentrations of natural chemical defenses and a greater diversity than plants from any other biome, thus they are potential sources of new medicines (Balick et al., 1996). It seems logical then to encourage studies on plants from these regions, especially since the major proportion of malaria-attributable deaths occur in sub-Saharan African regions (Fig. 1).

3. The search for new phytochemicals with antimalarial activity

In the last decade, there has been a renewed interest in indigenous medicine worldwide, arising from the realization that orthodox medicine is not widespread. In poor countries, the healthcare is often sustained by other practices based on cultural alternatives. In many developing countries, one-fifth of patients use indigenous herbal remedies to treat malaria (Willcox and Bodeker, 2004). Although modern medicine may be available in some communities, herbal medicines have often maintained popularity for historical and cultural reasons, in addition to their cheaper costs. The use of plant remedies has steadily increased worldwide in recent years, as well as the search for new phytochemicals that potentially could be developed as useful drugs for the treatment of malaria and other infectious diseases (Willcox, 1999).

Some decades ago, plants were randomly selected and screened for antimalarial activity. However, this procedure was laborious and did not yield much result. For example, in 1947, crude extracts of 600 species from 126 plant families were screened for their *in vivo* activity against avian malaria, i.e. *Plasmodium gallinaceum* in chicks and against *Plasmodium cathemerium* and *Plasmidium lophurae* in ducklings (Spencer et al., 1947), the available laboratory models then. Active extracts were obtained from species of 33 genera and consistently strong positive results obtained from species of the Simaroubaceae family. A better approach now used is selecting plants based on their ethnobotanical information. Plants are now selected based on their use in indigenous medicine against fever and/or malaria (Carvalho et al., 1991). This, to a great extent, has reduced the unnecessary waste of time and resources encountered in the former approach.

4. Nigerian medicinal plants used for malaria treatment

Nigeria has rich flora diversity and many of the plant species are used by some indigenous people for medicinal purposes. A larger number of medicinal plants are used to treat malaria in the Southern part of the country where rain forests exist and originate a humid tropical climate, with ideal conditions for persistent malaria transmission all year round (Fig. 2). Some plant species are used for

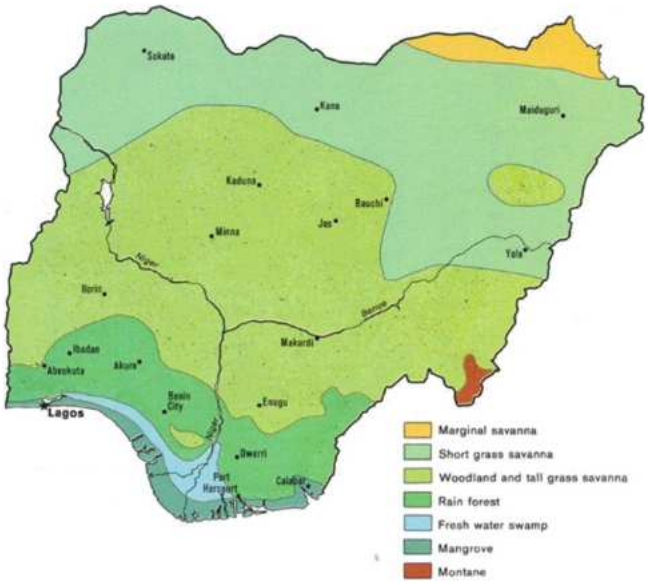

Fig. 2. Vegetation map of Nigeria [Perry-Castañeda Library Map Collection, University of Texas, USA (http://www.lib.utexas.edu/maps/nigeria.html)].

malaria treatment across all ethnic and cultural groups in the country, for example, *Alstonia boonei* (Apocynaceae) and *Azadirachta indica* (Meliaceae).

A systematic analysis study was carried out through a computer search of data on PubMed and ISI Web of Knowledge using key words (malaria; Nigeria; ethnobotany; antimalarial activity; medicinal plants; plant extracts; active compounds; and mode of action) for articles published from 1984 to 2008. Thus, this review is mainly based on the articles obtained from these databases. The articles selected concern studies on ethnobotany; *in vitro* and/or *in vivo* antimalarial activity of plants from Nigeria; isolated antimalarial compounds from these plants; probable mechanisms of action and references from relevant articles. Of the nine ethnobotanical studies in different parts of the country published in these data banks; only two were specifically on medicinal plants used for malaria treatment while the others were on medicinal plants used for various diseases including malaria. Medicinal plants used in Nigeria for malaria treatment are listed in Table 1 .

Alstonia boonei is a high tree of up to 33 m, with a straight and fluted stem, having no buttress roots. The species is highly priced, especially in situations where affordable antimalarial drugs are found ineffective, due to drug-resistant malaria parasites. The plant stem bark or leaves are administered as decoction or "teas" and sometimes as an ingredient in malaria "steam therapy". Recently, the stem bark extract was formulated into tablets, and made available as an antimalarial remedy (Majekodunmi et al., 2008).

Plants of the Meliaceae family are also commonly used for malaria treatment in Nigeria, like the species *Azadirachta indica, Khaya senegalensis* and *Khaya grandifoliola*. *Azadirachta indica* (Fig. 3) is called "neem tree" and is also used in other African countries as a decoction against fever and/or malaria. It is an evergreen, fast growing tree, up to 25 m in height and is used in traditional medical practice in form of an aqueous decoction of the leaves, stem bark and root (Obih and Makinde, 1985). Due to the importance of this plant as an antimalarial remedy in Nigeria, efforts were made to produce the tablet suspensions of the bark and leaf which exhibited high prophylactic, moderate suppressive and a very minimal curative schizonticidal effect in mouse model of malaria (Isah et al., 2003). *Khaya senegalensis* and *Khaya grandifoliola* are often planted by roadsides for shade. The decoctions of their stem barks are extensively used as antimalarial remedies but they seem to have adverse effects (Adebayo et al., 2003; Bumah et al., 2005). *Khaya* plants are so widely used for medicinal purposes that it is uncommon to find an intact tree near homes.

Morinda lucida (Rubiaceae), largely used in malaria treatment in Nigeria, is a tree of 9–18 m in height, bearing a dense crown of slender crooked branches (Avwioro et al., 2005). The wood is moderately coarse, open grained with a tendency to spiral, though not warping nor altering, fairly hard and of medium weight. The aerial parts, stem bark or root bark of *Morinda lucida* are widely used in West Africa to treat malaria and other tropical diseases. A seasonal variation in its antimalarial activity has been reported (Makinde et al., 1994). *Nauclea latifolia* (Rubiaceae) is a small spreading tree, essentially a savannah plant, used as aqueous decoction of the root bark against malaria.

Several other plants are used for malaria treatment in Nigeria, like *Quassia amara* and *Quassia undulata* (Simaroubaceae), largely used in the southwestern part of the country (Phillipson and Wright, 1991). *Quassia amara* (Fig. 3), called bitterwood tree, with 2–6 m in height, has the highest antimalarial reputation for curative and preventive purposes in the Simaroubaceae family. *Enantia chlorantha* (Annonaceae) is an ornamental tree, of up to 30 m in height, with dense foliage and spreading crown. Its stem bark is used against fever/malaria by traditional medicine practitioners in the forest regions. *Carica papaya* (Caricaceae), commonly referred to as pawpaw, is widely grown in the tropics for its edible fruit and also used as a weak decoction of its leaves against malaria. It is a small tree with a weak soft-wooden stem which is usually unbranched and hollow. *Fagara zanthoxyloides* (Rutaceae) has its root widely used as chewing stick in Nigeria and West Africa in general (Odebiyi and Sofowora, 1979). The aqueous extract of the root is used for malaria treatment by the indigenous people. *Spathodea campanulata* (Bignoniaceae), popularly known as African tulip tree is native to tropical Africa, though it has now been adapted to other tropical regions around the world, mostly because of its ornamental value. It is used in southwestern Nigeria for malaria treatment by drinking the decoction of its stem bark.

Most of these antimalarial plants are used in form of monotherapy, and only a few plants are taken together in combined therapies. An example is the multi-herbal extract referred to as 'Agbo-Iba' made up of *Cajanus cajan* (pigeon pea) leaf, *Euphorbia lateriflora* leaf, *Mangifera indica* leaf and bark, *Cassa alata* leaf, *Cymbopogon giganteus* leaf, *Nauclea latifolia* leaf, and *Uvaria chamae* bark (Nwabuisi, 2002). Another multi-herbal combination is the mixture of *Carica papaya* leaves, *Cymbopogon citratus* leaves, *Anacardium occidentale* leaves and *Azadirachta indica* leaves used in 'steam therapy', in which the patients are covered with a thick blanket and made to inhale the vapour from the cooking pot.

5. Scientific authentication of antimalarial activities of Nigerian medicinal plants

Pharmacological studies have demonstrated *in vitro* antiplasmodial and/or *in vivo* antimalarial activities of extracts from 45 plant species used in Nigerian folk medicine out of the 51 species tested. The publications with respect to both *in vivo* and *in vitro* tests herein cited taxonomically identified the plants with certified experts and voucher specimens were deposited in recognized herbaria. Fabricant and Farnsworth (2001) highlighted four standard approaches used for selecting plants: (1) random selection followed by chemical screening, (2) random selection followed by antimicrobial assays, (3) follow-up of antimicrobial activity reports and (4) follow-up of ethnomedical or traditional uses of plants against infectious diseases. Of these four approaches, the follow-up of ethnomedical or traditional uses of plants against malaria was the common approach used by various studies cited in this review.

Table 1
Medicinal plants used to treat fever and/or malaria in Nigeria.

Plant species (Family)	Part used	Geographical region	Reference
Abrus precatorius Linn. (Leguminosae-Caesalpinioideae)	Stem bark	Middle Belt, Northwest	Muhammad and Amusa (2005), Igoli et al. (2005)
Adansonia digitata Linn. (Bombacaceae)	Root	Southeast	Ibe and Nwufo (2005), Ajibesin et al., 2008
Afzelia africana Sm. (Leguminosae-Caesalpinioideae)	Stem bark	Northeast	Shuaibu et al. (2008)
Ageratum conyzoides Linn. (Compositae)	Whole plant	Southeast	Ehiagbonare (2007)
Alchornea cordifolia (Schum. & Thonn.) Müll.-Arg. (Euphorbiaceae)	Stem	Middle Belt	Tor-Anyiin et al. (2003)
Allanblackia floribunda Oliv. (Guttiferae)	Leaves, stem bark	Southwest	Kayode (2006)
Allium sativum Linn. (Alliaceae)	Bulb	Southwest	Odugbemi et al. (2007)
Alstonia boonei De Wild. (Apocynaceae)	Stem bark, roots, Leaves	All regions	Odugbemi et al. (2007), Ajibesin et al. (2008)
Anacardium occidentale Linn. (Anacardiaceae)	Leaves, stem bark	Southern regions	Kayode (2006), Ajibesin et al. (2008)
Annona senegalensis Pers. (Annonaceae)	Leaves	Middle Belt	Ajaiyeoba et al. (2006), Tor-Anyiin et al. (2003)
Anogeissus leiocarpus (DC.) Guill. & Perr. (Combretaceae)	Stem bark	Northern regions	Muhammad and Amusa (2005), Shuaibu et al. (2008)
Anthocleista djalonensis A.Chev. (Loganiaceae)	Leaves, stem bark	Southeast	Ajibesin et al. (2008)
Anthocleista vogelii Planch. (Loganiaceae)	Leaves	Middle Belt	Igoli et al. (2005)
Aspilia africana (P.Beauv.) C.D.Adams (Asteraceae)	Stem bark	Northwest	Muhammad and Amusa (2005)
Azadirachta indica A. Juss. (Meliaceae)	Leaves	All regions	Ehiagbonare (2007), Iwu et al. (1986)
Blighia sapida Konig (Sapindaceae)	Stem bark	Southwest	Kayode (2006)
Bridelia ferruginea Benth. (Euphorbiaceae)	Leaves, stem bark	Middle Belt	Tor-Anyiin et al. (2003)
Bridelia micrantha (Hochst.) Baill. (Euphorbiaceae)	Leaves	Middle Belt	Ajaiyeoba et al. (2006)
Cajanus cajan (Linn.) Millsp. (Leguminosae-Caesalpinioideae)	Leaves	Southwest	Ajaiyeoba et al. (2006)
Canna indica Linn. (Cannaceae)	Leaves	Southwest	Kayode (2006)
Carica papaya Linn. (Caricaceae)	Leaves	Middle Belt, Southeast	Ibe and Nwufo (2005), Tor-Anyiin et al. (2003)
Cassia occidentalis Linn. (Leguminosae-Caesalpinioideae)	Leaves	Northwest, Southeast	Ibe and Nwufo (2005), Muhammad and Amusa (2005)
Cassia siamea Lam. (Leguminosae-Caesalpinioideae)	Leaves, stem bark	Southwest	Ajaiyeoba et al. (2006)
Cassia sieberiana DC. (Leguminosae-Caesalpinioideae)	Leaves, root bark	Northeast	Shuaibu et al. (2008)
Cassia singueana Del. (Leguminosae-Caesalpinioideae)	Root bark	Northern regions	Adzu et al. (2003)
Cassytha filiformis Linn. (Lauraceae)	Twigs	Middle Belt	Igoli et al. (2005)
Celtis durandii Engl. (Ulmaceae)	Roots	Middle Belt, Southeast	Ibe and Nwufo (2005)
Chromolaena odorata Linn. King & Robinson (Compositae)	Root, leaves	Southwest	Odugbemi et al. (2007), Kayode (2006)
Cissus populnea Guill. & Perr. (Vitaceae)	Leaves	Northeast	Shuaibu et al., 2008
Citrus sinensis (Linn.) Osbeck (Rutaceae)	Stem	Southwest	Kayode (2006)
Crossopteryx febrifuga (Afzel. ex G. Don) Benth. (Rubiaceae)	Stem bark	Southwest	Elufioye and Agbedahunsi (2004)
Croton zambesicus Müll.-Arg. (Euphorbiaceae)	Leaves	Southeast	Ajibesin et al. (2008)
Crytolepis sanguinolenta (Lindl.) Schltr. (Asclepiadaceae)	Root	Southern regions	Boye and Ampofo (1983)
Curcuma Longa Linn. (Zingiberaceae)	Rhizome	Southwest	Odugbemi et al. (2007)
Cylicodiscus gabunensis (Taub.) Harms (Leguminosae-Mimosoideae)	Leaves	Southeast	Okokon et al. (2006b), Ajibesin et al. (2008)
Cymbopogon citratus (DC.) Stapf (Poaceae)	Leaves	Middle Belt, Southeast	Ajibesin et al. (2008), Tor-Anyiin et al. (2003)
Cymbopogon giganteus Chiov. (Poaceae)	Leaves	Southwest	Kimbi and Fagbenro-Beyioku (1996)
Daniellia ogea (Harms) Rolfe ex Holl. (Leguminosae-Caesalpinioideae)	Root	Southeast	Ajibesin et al. (2008)
Daniellia oliveri (Rolfe) Hutch. & Dalz. (Leguminosae-Caesalpinioideae)	Stem bark	Middle Belt, Northern regions	Muhammad and Amusa (2005), Shuaibu et al. (2008), Igoli et al. (2005)
Elaeis guineensis Jacq. (Palmae)	Root	Southwest	Kayode (2006)
Enantia chlorantha Oliv. (Annonaceae)	Stem bark	Middle Belt, Southern regions	Ajaiyeoba et al. (2006), Agbaje and Onabanjo (1991)
Erythrina senegalensis DC. (Leguminosae - Papilionoideae)	Stem bark	Middle Belt, Northern regions	Saidu et al. (2000), Etkin (1997), Igoli et al. (2005)
Eupatorium odoratum Linn. (Compositae)	Leaves	Southeast	Ajibesin et al. (2008)
Fagara zanthoxyloides Lam. (Rutaceae)	Root	Southwest	Kassim et al. (2005)
Ficus platyphylla Del. (Moraceae)	Stem bark	Northeast	Shuaibu et al. (2008)
Ficus thonningii Blume (Moraceae)	Stem bark	Northeast	Shuaibu et al. (2008)

Table 1 (*Continued*)

Plant species (Family)	Part used	Geographical region	Reference
Funtumia africana (Benth.) Stapf (Apocynaceae)	Root	Southwest	Odugbemi et al. (2007)
Gossypium arboreum Linn. (Malvaceae)	Leaves	Southwest	Ajaiyeoba et al. (2006)
Gossypium barbadense Linn. (Malvaceae)	Leaves	Southwest	Ajaiyeoba et al. (2006)
Gossypium hirsutum Linn. (Malvaceae)	Leaves	Southwest	Ajaiyeoba et al. (2006)
Guiera senegalensis J.F. Gmel. (Combretaceae)	Leaves	Southwest	Iwalewa et al. (1990)
Harungana madagascariensis Lam. ex Poir. (Guttiferae)	Stem bark	Southwest	Iwalewa et al., 2008
Hippocratea africana (Willd.) Loes. (Celastraceae)	Root	Southeast	Okokon et al. (2006a), Ajibesin et al. (2008)
Homalium letestui Pellegr. (Flacoutiaceae)	Root	Southeast	Okokon et al. (2006c)
Indigofera pulchra Willd. (Leguminosae - Papilionoideae)	Whole plant	Northeast	Adamu et al. (2005)
Khaya grandifoliola C.DC. (Meliaceae)	Stem bark	Middle Belt, Southwest	Agbedahunsi et al. (1998)
Khaya senegalensis (Desr.) A.Juss. (Meliaceae)	Stem bark	Middle Belt, Northeast, Southwest	Egwim et al. (2002), Shuaibu et al. (2008)
Lippia multiflora Moldenke (Verbenaceae)	Aerial part	Southwest	Ajaiyeoba et al. (2006)
Lonchocarpus cyanescens (Schum. & Thonn.) Benth. (Leguminosae- Papilionoideae)	Leaves	Northeast	Shuaibu et al. (2008)
Lophira alata Banks ex Gaertn. f. (Ochnaceae)	Leaves, stem bark, root, seed	Southwest	Kayode (2006)
Lophira lanceolata Van Tiegh. ex Keay. (Ochnaceae)	Leaves	Middle Belt	Igoli et al. (2005)
Mangifera indica Linn. (Anacardiaceae)	Leaves, stem bark	Middle Belt, Southwest	Ajaiyeoba et al. (2006), Awe et al. (1998), Igoli et al. (2005)
Milicia excelsa Welw. C.C. Berg (Moraceae)	Root, stem bark	Southwest	Odugbemi et al. (2007)
Mitragyna inermis (Willd.) O Ktze. (Rubiaceae)	Leaves	Middle Belt	Tor-Anyiin et al. (2003)
Momordica balsamina Linn. (Cucurbitaceae)	Leaves, Stem bark	Northern regions	Muhammad and Amusa (2005), Shuaibu et al. (2008)
Morinda lucida Benth. (Rubiaceae)	Leaves, stem bark	Middle Belt, Southwest	Tor-Anyiin et al. (2003), Awe and Makinde (1998)
Moringa oleifera Lam. (Moringaceae)	Leaves, stem bark, Root	Northeast	Shuaibu et al. (2008)
Nauclea latifolia Sm. (Rubiaceae)	Stem bark, root	Middle Belt, Southern regions	Ajaiyeoba et al. (2006), Ajibesin et al. (2008)
Newbouldia laevis Seem. (Bignoniaceae)	Leaves, root	Middle Belt	Tor-Anyiin et al. (2003)
Ocimum gratissimum Linn. (Labiatae)	Leaves	Middle Belt	Tor-Anyiin et al. (2003)
Parkia biglobosa (Jacq.) Benth. (Leguminosae-Mimosoideae)	Stem, fruit, leaves	Middle Belt, Southwest	Kayode (2006), Tor-Anyiin et al. (2003)
Pericopsis elata (Harms) Van Meeuwen (Leguminosae-Papilionoideae)	Leaves	Middle Belt	Ajaiyeoba et al. (2006)
Phyllanthus amarus Schum. & Thonn. (Euphorbiaceae)	Leaves	Southern regions	Ajibesin et al. (2008), Ajaiyeoba et al. (2003)
Picralima nitida (Staph) Th. & H.Dur. (Apocynaceae)	Stem bark, seed	Southeast	Ezeamuzie et al. (1994), Okokon et al. (2007a,b,c)
Piliostigma thonningii (Schumach.) Milne-Redh. (Leguminosae-Caesalpinioideae)	Leaves	Middle Belt, Southwest	Ajaiyeoba et al. (2006), Tor-Anyiin et al. (2003)
Prosopis Africana (Guill. & Perr.) Taub. (Leguminosae-Mimosoideae)	Leaves, stem bark	Northeast	Shuaibu et al. (2008)
Psidium guajava Linn. (Myrtaceae)	Stem bark, leaves	Middle Belt, Southwest	Ajaiyeoba et al. (2006), Tor-Anyiin et al. (2003)
Quassia amara Linn. (Simaroubaceae)	Leaves, Stem	Southwest	Ajaiyeoba et al. (1999)
Quassia undulata (Guill. & Perr.) D Dietr. (Simaroubaceae)	Leaves, stem	Southwest	Ajaiyeoba et al. (1999)
Rauvolfia vomitoria Afzel. (Apocynaceae)	Root, bark, leaves	Southwest	Odugbemi et al. (2007)
Saccharum officinarum Linn. (Poaceae)	Stem	Southeast	Ajibesin et al. (2008)
Scoparia dulcis Linn. (Scrophulariaceae)	Leaves	Middle Belt	Igoli et al. (2005)
Setaria megaphylla (Steud.) Dur. & Schinz (Poaceae)	Leaves	Southeast	Okokon et al. (2007c)
Sida acuta Burm. f. (Malvaceae)	Stem	Southeast	Obute (2005)
Solanum erianthum D Don (Solanaceae)	Leaves	Southwest	Makinde et al. (1987)
Solenostemon monostachyus (P. Beauv.) Briq. (Labiatae)	Leaves	Southeast	Ajibesin et al. (2008)
Spathodea campanulata P. Beauv. (Bignoniaceae)	Stem bark	Southwest	Makinde et al. (1988)
Sphenocentrum jollyanum Pierre (Menispermaceae)	Roots	Southwest	Odugbemi et al. (2007)
Stachytarpheta cayennensis (L.C. Rich) Val (Verbenaceae)	Leaves	Southeast	Okokon et al. (2008)
Stachytarpheta indica (Linn.) Vahl (Verbenaceae)	Leaves	Middle Belt	Igoli et al. (2005)
Sterculia setigera Del. (Sterculiaceae)	Stem bark	Middle Belt	Tor-Anyiin et al. (2003)
Stereospermum kunthianum Cham. (Bignoniaceae)	Leaves, stem bark	Middle Belt	Tor-Anyiin et al. (2003)

Table 1 (*Continued*)

Plant species (Family)	Part used	Geographical region	Reference
Striga hermonthica (Del.) Benth. (Scrophulariaceae)	Whole plant	Northern regions	Okpako and Ajaiyeoba (2004)
Tapinanthus sessilifolius (P. Beauv.) van Tiegh. (Loranthaceae)	Leaves	Northern regions	Okpako and Ajaiyeoba (2004)
Terminalia avicennoides Guill. & Perr. (Combretaceae)	Stem bark	Northeast	Shuaibu et al. (2008)
Terminalia latifolia Blanco (Combretaceae)	Leaves	Middle Belt	Ajaiyeoba et al. (2006)
Tetrapleura tetraptera (Schumm. & Thonn.) Taub. (Leguminosae-Mimosoideae)	Fruit	Southeast	Okokon et al. (2007b)
Tithonia diversifolia (Hemsl.) A.Gray (Compositae)	Leaves	Southwest	Ajaiyeoba et al. (2006), Elufioye and Agbedahunsi (2004)
Uvaria chamae P. Beauv. (Annonaceae)	Root	Southeast	Okokon et al. (2006a)
Vernonia amygdalia Del. (Compositae)	Leaves	Middle Belt, Southeast	Ehiagbonare (2007), Tor-Anyiin et al. (2003)
Vernonia cinerea (Linn.) Less. (Compositae)	Leaves, stem	Middle Belt	Igoli et al. (2005)
Zingiber officinale Rosc. (Zingiberaceae)	Rhizome	Southwest	Odugbemi et al. (2007)

An important factor to consider in the ethnomedical approach is the preparation of extract as described by the traditional healers in order to mimic as much as possible the way the herbal remedy is indigenously used. It was, however, observed that some of the studies did not carry out extraction with the common solvents (e.g. water and ethanol) used for preparation of indigenous medicine. They used solvents such as hexane, methylene chloride, and petroleum ether for extraction (Agbedahunsi et al., 1998; Bickii et al., 2000; Goffin et al., 2002; Cimanga et al., 2006), which are not acceptable in indigenous preparation of plant extracts and this, in a way, could affect the results obtained.

All publications with respect to antiplasmodial screening here cited have used classical methodologies such as the continuous culture of *Plasmodium falciparum* strains (Trager and Jensen, 1976); the *in vitro* antiplasmodial activity tests using radio-isotopic methods (Desjardins et al., 1979) or the microscopic methods; the *in vivo* antimalarial assays with reference to blood schizonticidal activity of plant extracts called the 4-day suppressive test (Peters, 1965) and Rane (Curative) test similar to that described by Ryley and Peters (1970), using rodent malaria model. All these approaches of testing plants and their isolated compounds have been recently reviewed (Krettli, 2009; Krettli et al., 2009). However, in this review, for *in vitro* studies, plant extracts considered active have IC_{50} values less than 10 mg/ml and those partially active with IC_{50} values less than 25 mg/ml (Carvalho et al., 1991), while for *in vivo* studies, extracts were considered active when parasitaemia was reduced at least by 50%.

Some of the active plants are listed in Table 2. Twenty-four plant species have only been tested *in vitro* against *Plasmodium falciparum* and reported to possess antiplasmodial activities. Some

Fig. 3. Nigerian medicinal plant parts used for malaria treatment in which the biological activities have been experimentally demonstrated.

Table 2
Nigerian medicinal plant extracts with antiplasmodial activities and their cytotoxicity values.

Plant species	Extraction solvent: IC_{50} of antimalarial plants (mg/ml) and (strains of *Plasmodium falciparum* used)[a]	IC_{50} of cytotoxicity test (mg/ml) and (cell-lines used)	Selectivity index: ratio cytotoxicity/activity[b]	References
Alchornea cordifolia	Ethanol: 2.30 (FcM29)	54.97 (Hela)	23.90	Mustofa et al. (2000)
	Ethanol: 3.06 (FcB1)		17.96	
	Ethanol: 3.15 (Nigerian)		17.45	
	Water: 3.50 (FcB1)		15.71	
	Water: 2.47 (Nigerian)		22.26	
Anogeissus leiocarpus	Methanol: 2.60 (FcB1)	71.90 (L-6)	27.65	Okpako and Ajaiyeoba (2004), Vonthron-Senecheau et al. (2003)
	Methanol: 10.94 (3D7)	≥1500.00 (NBMH)	≥121.00	Shuaibu et al. (2008)
	Methanol: 13.77 (K1)			
Aspilia africana	Ethyl acetate: 9.30 (D10)			Waako et al. (2007)
	Water: 22.70 (D10)			
	Methanol: 23.10 (D10)			
	Ethyl acetate: 11.50 (K1)			
Azadirachta indica	Ethanol: 2.40 (W2)		25.42	Benoit et al. (1996)
	Ethanol: 2.50 (D6)		24.40	MacKinnon et al. (1997), Kirira et al. (2006)
	Water: 4.17 (FcB1)		24.22	
Boswella dalzielli	Methanol: 14.59 (3D7)	≥1500.00 (NBMH)	≥101.00	Shuaibu et al., 2008
	Methanol: 15.10 (K1)			
Cassia occidentalis	Ethanol: 2.80 (N.S.)			Tona et al. (2004)
	Petroleum ether: 1.50 (N.S.)			
	Isoamyl alcohol: 8.60 (N.S.)			
	Chloroform: 2.90 (N.S.)			
Cocos nucifera (mestiço variety)	Hexane: 10.6 (W2)	379.00 (Hep G2)	35.00	Adebayo et al. (2010)
Cissus populnea	Methanol: 15.81 (3D7)	≥1500.00 (NBMH)	≥84.00	Shuaibu et al. (2008)
	Methanol: 19. 91 (K1)			
Erythrina senegalensis	Ethanol: 1.82 (K1)			Kamanzi Atindehou et al. (2004)
Fagara zanthoxyloides	Water: 4.90 (3D7)			Kassim et al. (2005)
Ficus platyhylla	Methanol: 15.28 (3D7)	≥1500.00 (NBMH)	≥103.00	Shuaibu et al. (2008)
	Methanol: 13.77 (K1)			
Ficus thonningii	Methanol: 14.09 (3D7)	≥1500.00 (NBMH)	≥77.00	Shuaibu et al. (2008)
Guiera senegalensis	Water: 0.79 (FcB1)	>25.00 (Thp1)	>25.00	Benoit et al. (1996), Ancolio et al. (2002)
Harungana madagascariensis	Methanol: 3.60(K1)			Ndjakou Lenta et al., 2007, Iwalewa et al. (2008)
	Ethanol: 0.05–0.52 (N.S.)			
Khaya grandifoliola	Methanol–methylene chloride: 13.23 (W2/Indochina clone)			Bickii et al. (2000), Agbedahunsi et al. (1998)
	Hexane: 1.40 (Multidrug resistant)			
	Hexane: 0.84 (Nigerian)			
Khaya senegalensis	Methanol: <5.00 (3D7)			El Tahir et al. (1999)
	Methanol: <5.00 (Dd2)			
Morinda lucida	Ethanol: 5.70			Awe and Makinde (1998), Cimanga et al. (2006)
	Methylene chloride: 5.20			
	Petroleum ether: 3.90			
Nauclea latifolia	Water: 0.60 (FcB1)	400.00 (Human melanoma	666.67	Benoit-Vical et al. (1998), Menan et al. (2006)
	Water: 0.70 (Nigerian)		571.43	
Proospis Africana	Methanol: 14.97 (3D7)	≥1500.00(NBMH)	≥99.00	Shuaibu et al. (2008)
	Methanol: 15.28 (K1)			
Quassia amara	Aqueous: 8.90 (FcB1)			Bertani et al. (2005)
Sida acuta	Ethanol: 3.90 (FcM29)			Banzouzi et al. (2004), Karou et al. (2003)
	Ethanol: 4.80 (Nigerian)			
	Water: 0.92 (FcM29)			
	Chloroform: 0.87 (FcM29)			
Terminalia avicennoides	Methanol: 12.28 (3D7)	≥1500.00(NBMH)	≥114.00	Shuaibu et al. (2008)
	Methanol: 14.09 (K1)			
Tithonia diversifola	Ether: 0.75 (FCA)			Goffin et al., 2002

[a] Extracts with IC_{50} values less than 10 mg/ml are considered active while those with IC_{50} values less than 25 mg/ml are considered partially active (Carvalho et al., 1991).
[b] Many of these plant extracts have not been tested for their cytotoxicities, thus their selectivity indices cannot be calculated.
N.S., not specified.

of them are: *Psidium guajava* (Nundkumar and Ojewole, 2002), *Alchornea cordifolia* (Banzouzi et al., 2002), *Aspilia africana* (Waako et al., 2007), *Cymbopogon citratus* (Bidla et al., 2004), *Fagara zanthoxyloides* (Kassim et al., 2005), *Sida acuta* (Karou et al., 2003), *Khaya senegalensis* (El Tahir et al., 1999), *Lippia multiflora* (Valentin et al., 1995), *Prosopis africana, Ficus platyphylla, Anogeissus leiocarpus, Ficus thonningii, Cissus populnea*, and *Terminalia avicennoides* (Shuaibu et al., 2008), *Mitragyna inermis* (Fiot et al., 2005), *Harungana madagascariensis* (Iwalewa et al., 2008), *Vernonia cinerea* (Chea et al., 2006) and *Nauclea latifolia* (Benoit-Vical et al., 1998). *Nauclea latifolia* inhibits *Plasmodium falciparum* erythrocytic cycle mainly at the end of schizogony (32nd to 48th hour) (Benoit-Vical et al.,

1998). It is noteworthy that all the *in vitro* studies cited in this review used whole organisms, which have been reported to have considerable advantages over the target-oriented options, most especially, they involve all targets and take bioavailability phenomena into account, such as ability of phytochemicals to cross the cell membrane (Cos et al., 2006). Moreover, most of the *in vitro* studies used well-characterized drug-sensitive/drug resistant parasite strains. A few authors, like Tona et al. (2004), however, did not specify the strains of parasite used. Many of the researchers in Nigeria who conducted *in vitro* studies had to collaborate with other laboratories outside the country. This may partly be as a result of insufficient facilities to support *in vitro* studies within the country and the high cost of such studies.

Fifteen medicinal plants and one herbal combination only have been screened *in vivo* for antimalarial activity against *Plasmodium berghei* or *Plasmodium yoelii* parasites and reported to be active (Table 3). They are: *Cylicodiscus gabunensis* (Okokon et al., 2006b), *Uvaria chamae* and *Hippocratea africana* (Okokon et al., 2006a), *Enantia chlorantha* and *Cymbopogon giganteus* (Agbaje and Onabanjo, 1991; Kimbi and Fagbenro-Beyioku, 1996), *Cymbopogon citratus* and *Ocimum gratissimum* (Tchoumbougnang et al., 2005), *Cassia singueana* (Adzu et al., 2003), *Stachytarpheta cayennensis* (Okokon et al., 2008), *Striga hermonthica* and *Tapinanthus sessilifolius* (Okpako and Ajaiyeoba, 2004), *Tetrapleura tetraptera* (Okokon et al., 2007b), *Setaria megaphylla* (Okokon et al., 2007c), *Phyllanthus amarus* (Dapper et al., 2007), *Homalium letestui* (Okokon et al., 2006c) and the plant formula 'Agbo-Iba' shown to protect mice against *Plasmodium yoelii nigeriensis* infection; the herbs used in this formula were decocted for 3 h and then administered to mice orally to evaluate the prophylactic and curative activities. Although the 'Agbo-Iba' formula was prophylactic and had no apparent significant side effects in mice, the formula had no curative activity against established infection (Nwabuisi, 2002). However, it must be noted that some of the doses used in these *in vivo* studies may not be of any practical use. For example, the aqueous extracts of *Azadirachta indica* caused 68% suppression in *Plasmodium yoelii nigeriensis*-infected mice at a very high dose of 800 mg/kg body weight. The toxicology of such high doses is seldom sufficiently well studied in animal experiments. Moreover, a few studies tested the extracts by intra-peritoneal and sub-cutaneous routes (Ajaiyeoba et al., 1999; Adzu et al., 2003), and were found efficacious because bioavailability is often better by these routes than by oral route. However, such routes are never used traditionally and results cannot be applied to oral administration. Furthermore, there is a greater risk of toxicity, though such studies reported that the tested extracts were non-toxic in murine model at the doses administered (Ajaiyeoba et al., 1999; Adzu et al., 2003).

Twelve Nigerian medicinal plants have been reported to exhibit activities *in vitro* and *in vivo* include *Azadirachta indica* (Obih and Makinde, 1985; MacKinnon et al., 1997; Isah et al., 2003), *Morinda lucida* (Obih et al., 1985; Awe and Makinde, 1998), *Khaya grandifoliola* (Agbedahunsi et al., 1998; Bickii et al., 2000), *Quassia amara* (Ajaiyeoba et al., 1999; Bertani et al., 2005), *Guiera senegalensis* (Iwalewa et al., 1990; Ancolio et al., 2002), *Tithonia diversifolia* (Goffin et al., 2002; Elufioye and Agbedahunsi, 2004), *Vernonia amygdalina* (Masaba, 2000; Abosi and Raseroka, 2003), *Cassia occidentalis* (Iwalewa et al., 1990; Tona et al., 1999; Zirihi et al., 2005), *Crossopteryx febrifuga* (Sanon et al., 2003; Elufioye and Agbedahunsi, 2004), *Spathodea campanulata* (Makinde et al., 1988; Dhanabalan et al., 2008), *Momordica balsamina* (Benoit-Vical et al., 2006) and *Picralima nitida* (Okokon et al., 2007a; Iwu and Klayman, 1992). *Azadirachta indica* antimalarial activity is attributed to a substantial oxidative stress during malaria infection; it affects all stages of maturation of the gametocytes, unlike artemisinin and primaquine that seem to affect only the immature stages (Dhar et al., 1998). *Picralima nitida* possesses a significant *in vivo* antimalarial activity in both early and established infections (Okokon et al., 2007a). Recently, we also tested both *in vitro* and *in vivo* a variety of *Cocos nucifera* (mestiço), used in Middle Belt region of Nigeria as an antimalarial remedy, and found the hexane extract to be active against *Plasmodium falciparum* W2 clone (an average IC_{50} of 10.6 mg/ml) and *Plasmodium berghei* NK65 (reducing parasitemia by 66% and 42% on days 5 and 11 post-infection respectively) (Adebayo et al., 2010). It should be noted, however, that some of these extracts exhibited very high antimalarial activity *in vitro* but displayed poor activity *in vivo*. A good example is *Azadirachta indica*, which is widely used around the world in indigenous medicine for the treatment of malaria. Its extract exhibited IC_{50} ranging from 2.4 to 4.17 mg/ml against various strains of *Plasmodium falciparum in vitro* (Benoit et al., 1996; MacKinnon et al., 1997), but required very high doses (e.g. 800 mg/kg body weight) to exhibit significant in vivo activity (Isah et al., 2003). Such high doses are not therapeutically meaningful.

6. Isolated compounds characterized as antimalarials in Nigerian medicinal plants

The active antimalarial principles of 16 plant species used in Nigerian folkmedicine for malaria treatment have been isolated (compounds considered to be active in this review have IC_{50} values of less than 5 mg/ml). Among the active compounds isolated (Table 4, Fig. 4), majority are alkaloids, followed by limonoids. Many of the isolated compounds have only been tested *in vitro* against *Plasmodium falciparum*, probably because of the little quantities isolated. Some of the alkaloids isolated are: (a) fagaronine, a benzophenanthridine alkaloid derived from the root extract of *Fagara zanthoxyloides;* inhibited *Plasmodium falciparum* growth *in vitro* at low IC_{50} (0.018 mg/ml) (Kassim et al., 2005); (b) palmatine and jatrorrhizine, protoberberine alkaloids isolated from *Enantia chlorantha* (Vennerstrom and Klayman, 1988); (c) indole and dihydroindole alkaloids isolated from *Picralima nitida*, the major constituents including akuammiline, akuammidine, akuammine, akuammigine, akuammicine, picraline, and alstonine (Ansa-Asamoah et al., 1990). Some of such alkaloids displayed *in vitro* antimalarial activity against *Plasmodium falciparum* comparable to chloroquine and quinine (Okunji et al., 2005), and IC_{50} values from 0.01 to 0.9 mg/mL, alstonine being the most active.

Limonoids isolated from medicinal plants have also been demonstrated to possess antimalarial activities, for example, gedunin from the wood extracts of *Azadirachta indica* plants collected in different locations (MacKinnon et al., 1997). The presence of an a, b -unsaturated ketone in ring A seems vital for its activity, as well as a 7a -acetate group; the furan ring also contributed to the described activity. However, gedunin did not inhibit *Plasmodium berghei* in mice (Bray et al., 1990). Four other limonoids were isolated from the leaves of *Azadirachta indica*, of which meldenin was the most active against *Plasmodium falciparum* (Joshi et al., 1998). Limonoids active against malaria parasites were isolated from *Khaya grandifoliola* (methylangolensate, 7-deacetylkhivorin, 1-deacetylkhivorin, and 6-acetylswietenolide and gedunin) (Bickii et al., 2000). The species *Khaya senegalensis* (bark, roots and seeds) yielded three limonoids of the mexicanolide type, with fissinolide and its 2,6-dihydroxy derivative exhibiting antiplasmodial activities *in vitro* (Khalid et al., 1998).

Other phytochemicals with antiplasmodial activities in Nigerian folkmedicinal plants are: (a) azadirachtin (a tetranortriterpenoid), which occurs in 4–6 g/kg amounts in neem seed kernels (Butterworth and Morgan, 1968), and inhibits the formation of mobile microgametes *in vitro*, an activity linked to the presence of a hemiacetal group at C-11 (Jones et al., 1994); (b) ursolic acid isolated from the stem bark of *Spathodea campanulata*, suppressed

Table 3
In vivo antimalarial activity and toxicity of active extracts of Nigerian medicinal plants.

Plant species	Extraction solvent	Plasmodium species	Dose (route of administration)	*In vivo* toxicity	References
Azadiracta indica	Water	*Py*	800 mg/kg/day (oral)	Non-toxic in murine model	Isah et al. (2003)
Cassia singueana	Methanol	*Pb*	200 mg/kg/day (sub-cutaneous)	Non-toxic in murine model	Adzu et al. (2003)
Crossopteryx febrifuga	Ethanol	*Pb*	100 mg/kg/day (oral)	Not available	Elufioye and Agbedahunsi (2004)
Morinda lucida	Ethanol Methylene Chloride Petroleum ether	*Pb*	200 mg/kg/day	Not available	Cimanga et al. (2006)
Quassia amara	Hexane	*Pb*	100 mg/kg/day (intraperi-toneal)	Non-toxic in murine model	Ajaiyeoba et al. (1999)
	Aqueous	*Py*	90 mg/kg/day	Not available	Bertani et al., 2005
Picralima nitida	Ethanol	*Pb*	115 mg/kg/day	Not available	Okokon et al. (2007a,b,c)
Striga hermonthica	Methanol	*Pb*	400 mg/kg/day	Not available	Okpako and Ajaiyeoba (2004)
Tapinanthus sessilifolius	Methanol	*Pb*	400 mg/kg/day	Not available	Okpako and Ajaiyeoba (2004)
Tithonia diversifolia	Ethanol	*Pb*	100 mg/kg/day (oral)	Not available	Elufioye and Agbedahunsi (2004)

Extracts considered active reduced parasitaemia by at least 50%. *Pb* – *Plasmodium berghei*; *Py* – *Plasmodium yeolii*.

infection and prolonged the survival of mice infected with *Plasmodium berghei* (Amusan et al., 1996); (c) anthraquinones from *Morinda lucida*, the most active being damnacanthal; structure–activity studies showed that an aldehyde group at C-2 and a phenolic hydroxy group at C-3 enhanced activity against *Plasmodium falciparum* (Koumaglo et al., 1992; Sittie et al., 1999); (d) sesquiterpene lactone, Tagitinin C, present in the leaves of *Tithonia diversifolia* was active against *Plasmodium falciparum* (Goffin et al., 2002); (e) Ajoene, a metabolite of *Allium sativum*, was active against *Plasmodium berghei* in mice (Perez et al., 1994); (f) Simalikalactone D was identified to be responsible for the antimalarial activity of *Quassia amara* leaves (Bertani et al., 2006).

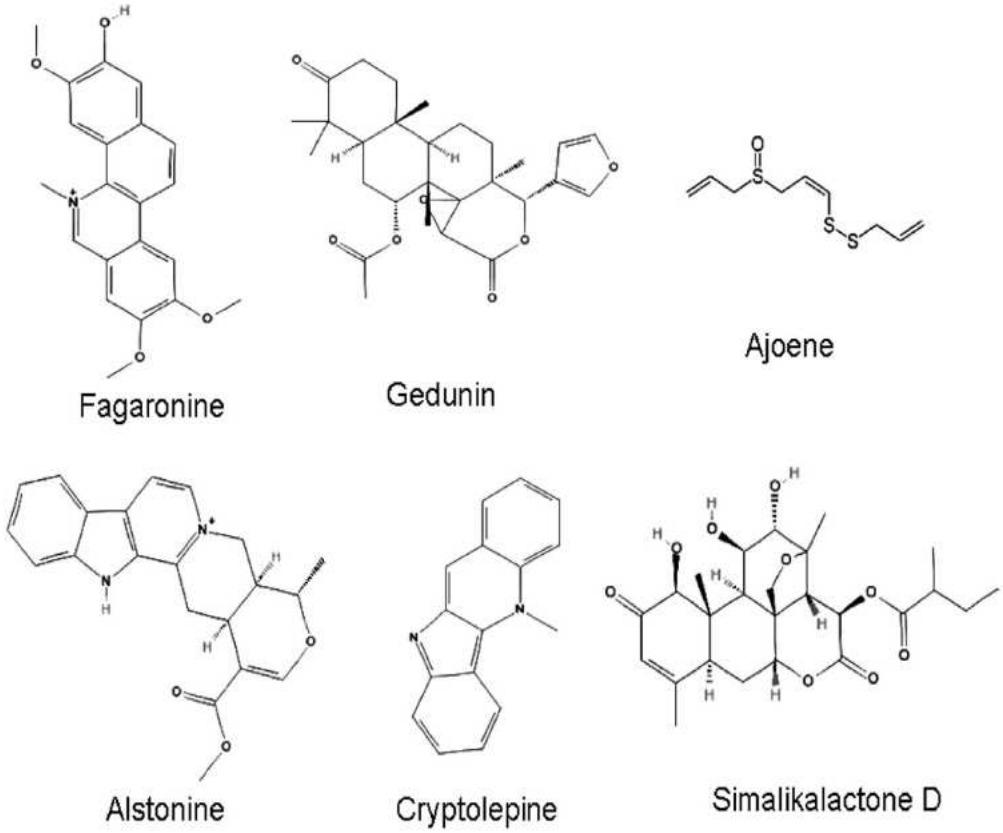

Fig. 4. Structures of some isolated antimalarial compounds from plants used in Nigeria for malaria treatment.

Table 4
Antimalarial activity and cytotoxicity of compounds from Nigerian medicinal plants.

Plants species	Isolated active compounds	Antiplasmodial activity, IC_{50} (mg/ml) and strains used	Cytotoxicity IC_{50} (mg/ml) and cell-lines used	Selectivity index (cytotoxicity/activity)[a]	References
Abrus precatorius	Abruquinone B	1.500 (K1)			Limmatvapirat et al. (2004)
Alchornea cordifolia	Ellagic acid	0.080 (FcM29)	6.200 (Hela)	77.500	Banzouzi et al. (2002)
		0.140 (Nigerian)	6.200 (Hela)	44.290	
Allium sativum	Ajoene[b]				Perez et al. (1994), Coppi et al. (2006)
	Allicin[b]				
Azadiracta indica	Gedunin	0.039 (D6)	2.300 (KB)	58.980	MacKinnon et al. (1997), Devi et al. (2001), Bray et al. (1990), Joshi et al. (1998), Biswas et al. (2002), and Saxena et al. (2003)
		0.020 (W2)	2.300 (KB)	115.000	
Cassia siamea	Emodin	5.000(K1)			Ajaiyeoba et al. (2008), Morita et al. (2007), and Oshimi et al. (2008)
	Lupeol	5.000(K1)			
	Cassiarin A	0.020[c]			
Fagara zanthoxyloides	Fagaronine	0.018(3D7)			Kassim et al. (2005), Odebiyi and Sofowora (1979)
Guiera senegalensis	Harman	2.200 (D6)	49.000 (THP1)	22.270	Ancolio et al. (2002), Combier et al., 1977
	Tetrahydroharman	1.300 (W2)	49.000 (THP1)	37.700	
	Guieranone A	3.900 (D6)	90.000 (THP1)	23.080	
		1.400 (W2)	90.000 (THP1)	64.280	
Khaya grandifoliola	Gedunin	1.250 (W2/Indochina clone)			Agbedahunsi and Elujoba (1998), Agbedahunsi et al. (1998), and Bickii et al. (2000)
Khaya senegalensis	2,6-Dihydroxyfissinolide,	0.120 (3D7)[c]			Khalid et al. (1998)
Morinda lucida	Urosilic acid[a]	3.100 (CQ-sensitive)			Cimanga et al. (2006)
Picralima nitida	Akuammicine,	0.450 (D6)			Iwu and Klayman (1992), Okunji et al. (2005), Okokon et al. (2007a,b,c), and François et al. (1996)
	Akuammine,	0.730 (W2)			
	Alstonine,	0.950 (D6)			
	Picraline,	0.660 (W2)			
	Picratidine,	0.017 (D6)			
	Picranitidine	0.038 (W2)			
	ψ-Akuammigine	0.440 (D6)			
		0.530 (W2)			
		0.800 (D6)			
		0.920 (W2)			
		0.040 (D6)			
		0.030 (W2)			
		0.420 (D6)			
		0.100 (W2)			
Quassia amara	Simalikalactone D[b]	0.010 (FcB1)[c]			Bertani et al. (2006)
Quassia indica	Samaderines X	0.015 (K1)[c]			Kitagawa et al. (1996)
	Samaderines Z	0.071 (K1)[c]			
	Samaderines B	0.071 (K1)[c]			
	Samaderines E	0.210 (K1)[c]			
Sida acuta	Cryptolepine	0.114 (K1)		9.000	Banzouzi et al. (2004), Karou et al. (2003), and Frederich et al. (2008)
	Alkaloids	0.050 (N.S.)			
Spathodea campanulata	Ursolic acid[b]				Amusan et al. (1996), Steele et al. (1999)
Tithonia diversifola	Tagitinin C	0.330 (FCA)	0.710 (HTC-116)	2.150	Goffin et al. (2002)

[a] Many of these isolated compounds have not been tested for their cytotoxicities, thus their selectivity indices cannot be calculated. Many of them also have not been tested for antimalarial activity in vivo.
[b] Molecules have been reported to be active *in vivo* against rodent *Plasmodium* species, causing at least 50% reduction in parasitemia.
[c] IC_{50} value expressed in mM.
N.S., not specified.

However, the possibility that the *in vitro* data presented in the studies with these phytochemicals could be misleading cannot be overlooked because certain natural products are metabolized and the pharmacokinetics of the individual natural products are often totally ignored. Compounds referred to as being active *in vitro* may actually be inactive *in vivo*, e.g. gedunin. It would be extremely helpful if more pharmacokinetic studies could be performed with these phytochemicals, though it must be appreciated that most of the time, small quantities of these compounds are isolated which limits their *in vivo* studies. Moreover, some of the phytochemicals which have been reported to be active *in vivo*, exhibited such activities at very high doses that may not be of any meaningful therapeutic use. An example is urosilic acid reported to cause 97.7% chemosuppression in *Plasmodium berghei berghei*–infected mice but at a dose of 200 mg/kg body weight (Cimanga et al., 2006). Also, many of these compounds have not been tested for their cytotoxicities. This seriously limits their potentials as future antimalarial drugs. As Gertsch (2009) pointed out, the molecular architecture (carbon scaffold, heteroatoms, functional groups, multiple stereocenters, etc.) of natural products greatly facilitates protein interactions probably because natural products have been phylogenetically selected in a protein environment. Therefore, protein binding interactions of natural products may not be linear with concentration but exponential, implying that high concentrations are always likely to generate a response as multiple proteins are targeted, almost non-selectively. Thus, more data with respect to

the cytotoxicities of the phytochemicals are still needed in order to calculate their selectivity indices (cytotoxicity/activity), which will then serve as a strong basis for their being considered as potential antimalarial drugs. Some of these active compounds which have even been tested for cytotoxicity have been found to be toxic, having very low selectivity indices (e.g. tagitinin C and cryptolepine, Table 4). All these have brought limitations on some of the isolated compounds being considered as lead molecules for antimalarial drug development.

6.1. Mechanisms of action suggested for isolated antimalarial compounds from medicinal plants used in Nigeria

Various mechanisms of action have been postulated for the isolated antimalarial compounds but the mechanisms of action listed below are those obtained from direct study of the compounds on the parasite. The suggested mechanisms of action for some antimalarial compounds isolated from plants are: (i) inhibition of hemozoin polymerization in the parasite, e.g. cryptolepine—an indole alkaloid isolated from *Sida acuta* and *Cryptrolepis sanguinolenta* (Banzouzi et al., 2004; Onyeibor et al., 2005; Karou et al., 2007a,b); (ii) intercalation with the parasite DNA as in the case of cryptolepine (Kirby et al., 1994); (iii) inhibition of *Plasmodium falciparum* lactate dehydrogenase (*pf*LDH), an essential enzyme for energy generation within the parasite through glycolysis, e.g. gossypol, a disesquiterpene extracted from seeds of *Gossypium* species (Royer et al., 1986; Gomez et al., 1997); (iv) alkylation e.g. gedunin (Arnason et al., 2004); (v) interference with the formation of mitotic spindles and the assembly of microtubules into typical axonemes in gametes, thus inhibiting the formation of mobile micmrogametes e.g. azadirachtin (Jones et al., 1994; Billker et al., 2002); (vi) inhibition of proteolytic processing of circumsporozoite protein by a parasite-derived cysteine protease, thereby preventing sporozoite invasion of host cells e.g. allicin, a cysteine protease inhibitor (Coppi et al., 2006).

7. Conclusion

The various ethnobotanical surveys carried out in Nigeria have allowed the description of a large number of plants used by the indigenous populations to treat different diseases, especially malaria in the endemic areas of transmission, as herein reviewed. The species investigated for antimalarial activity and their potentials as sources of new antimalarial compounds and new drug leads are herein discussed. Several purified compounds have been isolated and evaluated for their antimalarial activity. Efforts and resources to improve the malaria control programs have increased in Nigeria, where the burden of malaria is greatest in Africa due to the large population. It is in light of these facts that our present studies are directed towards compounds isolated from Nigerian plants with the hope that they will be useful in rolling back this disease. Since malaria is mostly endemic in areas naturally endowed with the rain forests, one hopes that these discoveries of active compounds from plants will generate more effective drugs, affordable and available to the rural people who are mostly at risk of the disease morbidity.

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References

Abosi, A.O., Raseroka, B.H., 2003. *In vivo* antimalarial activity of *Vernonia amygdalina*. British Journal of Biomedical Science 60, 89–91.
Adamu, H.M., Abayeh, O.J., Agho, M.O., Abdullahi, A.L., Uba, A., Dukku, H.U., Wufem, B.M., 2005. An ethnobotanical survey of Bauchi State herbal plants and their antimicrobial activity. Journal of Ethnopharmacology 99, 1–4.
Adebayo, J.O., Krettli, L.G., Paula, R.C., Felipe, L.M., Santana, A.E.G., Krettli, A.U., 2010. Evaluation of the antimalarial activity and toxicity potentials of husk fiber extracts from *Cocos nucifera*, a medicinal plant used in Nigeria to treat human malaria. In press.
Adebayo, J.O., Malomo, S.O., 2002. The effect of coadministration of dihydroartemisinin with vitamin E on the activities of cation ATPases in some rat tissues. Nigerian Journal of Pure and Applied Sciences 17, 1245–1252.
Adebayo, J.O., Yakubu, M.T., Egwim, E.C., Owoyele, B.V., Enaibe, B.U., 2003. Effect of ethanolic extract of *Khaya senegalensis* on some biochemical parameters of rat kidney. Journal of Ethnopharmacology 88, 69–72.
Adzu, B., Abbah, J., Vongtau, H., Gamaniel, K., 2003. Studies on the use of *Cassia singueana* in malaria ethnopharmacy. Journal of Ethnopharmacology 88, 261–267.
Agbaje, E.O., Onabanjo, A.O., 1991. The effects of extracts of *Enantia chlorantha* in malaria. Annals of Tropical Medicine and Parasitology 85, 585–590.
Agbedahunsi, J.M., Elujoba, A.A., Makinde, J.M., Oduda, A.M.J., 1998. Antimalarial activity of *Khaya grandifoliola* stem-bark. Pharmaceutical Biology 36, 8–12.
Agbedahunsi, J.M., Elujoba, A.A., 1998. Grandifolin from *Khaya grandifoliola* stem bark. Nigerian Journal of Natural Product and Medicine 2, 34–36.
Ajaiyeoba, E.O., Abalogu, U.I., Krebs, H.C., Oduola, A.M.J., 1999. *In vivo* antimalarial activities of *Quassia amara* and *Quassia undulata* plant extracts in mice. Journal of Ethnopharmacology 67, 321–325.
Ajaiyeoba, E.O., Abiodun, O.O., Falade, M.O., Ogbole, N.O., Ashidi, J.S., Happi, C.T., Akinboye, D.O., 2006. *In vitro* cytotoxicity studies of 20 plants used in Nigerian antimalarial ethnomedicine. Phytomedicine 13, 295–298.
Ajaiyeoba, E.O., Ashidi, J.S., Okpako, L.C., Houghton, P.J., Wright, C.W., 2008. Antiplasmodial compounds from *Cassia siamea* stem bark extract. Phytotherapy Research 22, 254–255.
Ajaiyeoba, E.O., Oladepo, O., Fawole, O.I., Bolaji, O.M., Akinboye, D.O., Ogundahunsi, O.A., Falade, C.O., Gbotosho, G.O., Itiola, O.A., Happi, T.C., Ebong, O.O., Ononiwu, I.M., Osowole, O.S., Oduola, O.O., Ashidi, J.S., Oduola, A.M., 2003. Cultural categorization of febrile illnesses in correlation with herbal remedies used for treatment in Southwestern Nigeria. Journal of Ethnopharmacology 85, 179–185.
Ajibesin, K.K., Ekpo, B.A., Bala, D.N., Essien, E.E., Adesanya, S.A., 2008. Ethnobotanical survey of Akwa Ibom State of Nigeria. Journal of Ethnopharmacology 115, 387–408.
Afonso, A., Hunt, P., Cheesman, S., Alves, A.C., Cunha, C.V., do Rosario, V., Cravo, P., 2006. Malaria parasites can develop stable resistance to artemisinin but lack mutations in candidate genes atp6 (encoding the sarcoplasmic and endoplasmic reticulum Ca^{2+} ATPase), tctp, mdr1, and cg10. Antimicrobial Agents Chemotherapy 50, 480–489.
Alonso, P.L., Sacarlal, J., Aponte, J.J., Leach, A., Macete, E., Aide, P., Sigauque, B., Milman, J., Mandomando, I., Bassat, Q., Guinovart, C., Espasa, M., Corachan, S., Lievens, M., Navia, M.M., Dubois, M.C., Menendez, C., Dubovsky, F., Cohen, J., Thompson, R., Ballou, W.R., 2005. Duration of protection with RTS, S/AS02A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. Lancet 366, 2012–2018.
Amusan, O.O.G., Adesogan, E.K., Makinde, J.M., 1996. Antimalarial active principles of *Spathodea campanulata* stem bark. Phytotherapy Research 10, 692–693.
Ancolio, C., Azas, N., Mahiou, V., Ollivier, E., Di Giorgio, C., Keita, A., Timon-David, P., Balansard, G., 2002. Antimalarial activity of extracts and alkaloids isolated from six plants used in traditional medicine in Mali and Sao Tome. Phytotherapy Research 16, 646–649.
Ansa-Asamoah, R., Kapadia, G.J., Lloyd, H.A., Sokoloski, E.A., 1990. Picratidine, a new indole alkaloid from *Picralima nitida* seeds. Journal of Natural Products 53, 975–977.
Aponte, J.J., Aide, P., Renom, M., Mandomando, I., Bassat, Q., Sacarlal, J., Manaca, M.N., Lafuente, S., Barbosa, A., Leach, A., Lievens, M., Vekemans, J., Sigauque, B., Dubois, M.C., Demoitié, M.A., Sillman, M., Savarese, B., McNeil, J.G., Macete, E., Ballou, W.R., Cohen, J., Alonso, P.L., 2007. Safety of the RTS, S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. Lancet 370, 1543–1551.
Arnason, J.T., Guillet, G., Durst, T., 2004. Phytochemical diversity of insect defenses in tropical and temperate plant families. In: Carde, R.T., Millar, J.G. (Eds.), Advances in Insect Chemical Ecology. Cambridge University Press, pp. 1–10.
Avwioro, O.G., Aloamaka, P.C., Ojianya, N.U., Oduola, T., Ekpo, E.O., 2005. Extracts of Pterocarpus osun as a histological stain for collagen fibres. African Journal of Biotechnology 5, 460–462.
Awe, S.O., Makinde, J.M., 1998. Evaluation of sensitivity of *Plasmodium falciparum* to *Morinda lucida* leaf extract sample using rabbit *in vitro* microtest technique. Indian Journal of Pharmacology 30, 51–53.
Awe, S.O., Olajide, O.A., Oladiran, O.O., Makinde, J.M., 1998. Antiplasmodial and antipyretic screening of *Mangifera indica* extract. Phytotherapy Research 12, 437–438.
Baird, J.K., Caneta-Miguel, E., Masba, S., Bustos, D.G., Abrenica, J.A., Layawen, A.V., Calulut, J.M., Leksana, B., Wignall, F.S., 1996. Survey of resistance to chloroquine of *falciparum* and *vivax* malaria in Palawan, The Philippines. Transactions of the Royal Society of Tropical Medicine and Hygiene 90, 413–414.

Balick, M.J., Elizabetsky, E., Laird, S.A., 1996. Medicinal Resources of the Tropical Rain Forest. Columbia University Press, New York.
Banzouzi, J.T., Prado, R., Menan, H., Valentin, A., Roumestan, C., Mallie, M., Pelissier, Y., Blache, Y., 2002. *In vitro* antiplasmodial activity of extracts of *Alchornea cordifolia* and identification of an active constituent: ellagic acid. Journal of Ethnopharmacology 81, 399–401.
Banzouzi, J.T., Prado, R., Menan, H., Valentin, A., Roumestan, C., Mallie, M., Pelissier, Y., Blache, Y., 2004. Studies on medicinal plants of Ivory Coast: investigation of *Sida acuta* for *in vitro* antiplasmodial activities and identification of an active constituent. Phytomedicine 11, 338–341.
Bejon, P., Lusingu, J., Olotu, A., Leach, A., Lievens, M., Vekemans, J., Mshamu, S., Lang, T., Gould, J., Dubois, M.-C., Demoitié, M.-A., Stallaert, J.-F., Vansadia, P., Carter, T., Njuguna, P., Awuondo, K.O., Malabeja, A., Abdul, O., Gesase, S., Mturi, N., Drakeley, C.J., Savarese, B., Villafana, T., Ballou, W.R., Cohen, J., Riley, E.M., Lemnge, M.M., Marsh, K., von Seidlein, L., 2008. Efficacy of RTS, S/AS01E vaccine against malaria in children 5 to 17 months of age. New England Journal of Medicine 359, 2521–2532.
Benoit, F., Valentin, A., Pelissier, Y., Diafouka, F., Marion, C., Kone-Bamba, D., Kone, M., Mallie, M., Yapo, A., Bastide, J.M., 1996. *In vitro* antimalarial activity of vegetal extracts used in West African traditional medicine. American Journal of Tropical Medicine and Hygiene 54, 67–71.
Benoit-Vical, F., Grellier, P., Abdoulaye, A., Moussa, I., Ousmane, A., Berry, A., Ikhiri, K., Poupat, C., 2006. *In vitro* and *in vivo* antiplasmodial activity of *Momordica balsamina* alone or in a traditional mixture. Chemotherapy 52, 288–292.
Benoit-Vical, F., Valentin, A., Cournac, V., Pélissier, Y., Mallié, M., Bastide, J.M., 1998. *In vitro* antiplasmodial activity of stem and root extracts of *Nauclea latifolia* S.M. (Rubiaceae). Journal of Ethnopharmacology 61, 173–178.
Bertani, S., Bourdy, G., Landau, I., Robinson, J.C., Esterre, P., Deharo, E., 2005. Evaluation of French Guiana traditional antimalarial remedies. Journal of Ethnopharmacology 98, 45–54.
Bertani, S., Houël, E., Stien, D., Chevolot, L., Jullian, V., Garavito, G., Bourdy, G., Deharo, E., 2006. Simalikalactone D is responsible for the antimalarial properties of an Amazonian traditional remedy made with *Quassia amara* L. (Simaroubaceae). Journal of Ethnopharmacology 108, 155–157.
Bickii, J., Nijifutie, N., Foyere, J.A., Basco, L.K., Ringwald, P., 2000. *In vitro* antimalarial activity of limonoids from *Khaya grandifoliola* C.D.C (Meliaceae). Journal of Ethnopharmacology 69, 27–33.
Billker, O., Shaw, M.K., Jones, I.W., Ley, S.V., Mordue (Luntz), A.J., Sinden, R.E., 2002. Azadirachtin disrupts formation of organised microtubule arrays during microgametogenesis of Plasmodium berghei. Journal of Eurkaryotic Microbiology 49, 489–497.
Biswas, K., Chattopadhyay, I., Banerjee, R.K., Bandyopadhyay, U., 2002. Biological activities and medicinal properties of neem (*Azadirachta indica*). Current Science 82, 1336–1345.
Bidla, G., Titanji, V.P.K., Joko, B., El-Ghazali, G., Bolad, A., Berzins, K., 2004. Antiplasmodial activity of seven plants used in African folk medicine. Indian Journal of Pharmacology 36, 245–246.
Boareto, A.C., Muller, J.C., Bufalo, A.C., Botelho, G.G.K., de Araujo, S.L., Foglio, M.A., de Morais, R.N., Dalsenter, P.R., 2008. Toxicity of artemisinin [*Artemisia annua* L.] in two different periods of pregnancy in Wistar rats. Reproductive Toxicology 25, 239–246.
Borstnik, K., Paik, I.H., Shapiro, T.A., Posner, G.H., 2002. Antimalarial chemotherapeutic peroxides: artemisinin, yingzhaosu A and related compounds. International Journal of Parasitology 32, 1661–1667.
Boye, G.L., Ampofo, O., 1983. Proceedings of the First International Symposium on cryptolepine. Abstract No. 4 ,. University of Science and Technology, Kumasi, Ghana.
Bray, D.H., Warhurst, D.C., Connolly, J.D., O'Neill, M.J., Phillipson, J.D., 1990. Plants as sources of antimalarial drugs. Part 7. Activity of some species of Meliaceae and their constituent limonoids. Phytotherapy Research 4, 29–35.
Bruce-Chwatt, L.J., 1982. Qinghaosu: a new antimalarial. British Medical Journal (Clinical Research Ed.) 284, 767–768.
Bumah, V.V., Essien, E.U., Agbedahunsi, J.M., Ekah, O.U., 2005. Effects of *Khaya grandifoliola* (Meliaceae) on some biochemical parameters in rats. Journal of Ethnopharmacology 102, 446–449.
Butterworth, J.H., Morgan, E.D., 1968. Isolation of a substance that suppresses feeding in locusts. Journal of Chemical Society, Chemical Communication, 23–24.
Carvalho, L.H., Brandão, M.G.L., Santos-Filho, D., Lopes, J.L.C., Krettli, A.U., 1991. Antimalarial activity of crude extracts from Brazilian plants studied in vivo in *Plasmodium berghei*-infected mice and in vitro against Plasmodium falciparum in culture. Brazilian Journal of Medical and Biological Research 24, 1113–1123.
Chea, A., Hout, S., Long, C., Marcourt, L., Faure, R., Azas, N., Elias, R., 2006. Antimalarial activity of sesquiterpene lactones from *Vernonia cinerea*. Chemical and Pharmaceutical Bulletin (Tokyo) 54, 1437–1439.
Cimanga, R.K., Tona, G.L., Mesia, G.K., Kambu, O.K., Bakana, D.P., Kalenda, P.D.T., Penge, A.O., Muyembe, J-J.T., Totté, J., Pieters, L., Vlietinck, A.J., 2006. Bioassay-guided isolation of antimalarial triterpenoid acids from the leaves of *Morinda lucida*. Pharmaceutical Biology 44, 677–681.
Combier, H., Becchi, M., Cavé, A., 1977. Alcaloïdes du *Guiera senegalensis* Lam. Plantes Médicinales et Phytothérapie 11, 251–253.
Coppi, A., Cabinian, M., Mirelman, D., Sinnis, P., 2006. Antimalarial activity of allicin, a biologically active compound from garlic cloves. Antimicrobial Agents Chemotherapy 50, 1731–1737.
Cos, P., Vlietinck, A.J., Berghe, D.V., Maes, L., 2006. Anti-infective potential of natural products: how to develop a stronger in vitro 'proof-of-concept'. Journal of Ethnopharmacology 106, 290–302.
Dapper, D.V., Aziagba, B.N., Ebong, O.O., 2007. Antiplasmodial effects of the aqueous extract of *Phyllanthus amarus* Schumach and Thonn against *Plasmodium berghei* in Swiss albino mice. Nigerian Journal of Physiological Science 22, 19–25.
Desjardins, R.E., Canfield, C.J., Haynes, J.D., Chulay, J.D., 1979. Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique. Antimicrobial Agents and Chemotherapy 16, 710–718.
Devi, C.U., Valecha, N., Atul, P.K., Pillai, C.R., 2001. Antiplasmodial effect of three medicinal plants: a preliminary study. Current Science 80, 917–919.
Dhanabalan, R., Doss, A., Jagadeeswari, M., Karthic, R., Palaniswamy, M., Angayarkanni, J., 2008. Preliminary phytochemical screening and antimalarial studies of *Spathodea campanulatum* P. Beauv leaf extracts. Ethnobotanical Leaflets 12, 811–819.
Dhar, R., Zhang, K., Talwar, G.P., Garg, S., Kumar, N., 1998. Inhibition of the growth and development of asexual and sexual stages of drug-sensitive and resistant strains of the human malaria parasite *Plasmodium falciparum* by Neem (*Azadirachta indica*) fractions. Journal of Ethnopharmacology 61, 31–39.
Egwim, E.C., Badru, A.A., Ajiboye, K.O., 2002. Testing pawpaw (*Carica papaya*) leaves and African Mahogany (*Khaya senegalensis*) bark for antimalarial activities. NISEB Journal 2, 37–39.
Ehiagbonare, J.E., 2007. Vegetative propagation on some key malaria medicinal plants in Nigeria. Scientific Research and Essay 2, 37–39.
El Tahir, A., Satti, G.M., Khalid, S.A., 1999. Antiplasmodial activity of selected Sudanese medicinal plants with emphasis on *Maytenus senegalensis* (Lam.) Exell. Journal of Ethnopharmacology 64, 227–233.
Elufioye, T.O., Agbedahunsi, J.M., 2004. Antimalarial activities of *Tithonia diversifolia* (Asteraceae) and *Crossopteryx febrifuga* (Rubiaceae) on mice *in vivo*. Journal of Ethnopharmacology 93, 167–171.
Etkin, L.N., 1997. Antimalarial plants used by the Hausas in Northern Nigeria. Tropical Doctor 27, 1–5.
Ezeamuzie, K., Ojinnaka, M.C., Uzogara, E.O., Orji, S.E., 1994. Antiinflammatory, antipyretic and antimalarial activities of West African medicinal plant, *Picralima nitida*. African Journal of Medicine and Medical Sciences 23, 85–90.
Fabricant, D.S., Farnsworth, N.R., 2001. The value of plants used in traditional medicine for drug discovery. Environmental Health Perspectives 109, 69–75.
Federal Ministry of Health, 2004. National Antimalarial Treatment Policy. Federal Ministry of Health, Abuja, Nigeria.
Frederich, M., Tits, M., Angenot, L., 2008. Potential antimalarial activity of indole alkaloids. Transactions of the Royal Society of Tropical Medicine and Hygiene 102, 11–19.
Fiot, J., Baghdikian, B., Boyer, L., Mahiou, V., Azas, N., Gasquet, M., Timon-David, P., Balansard, G., Ollivier, E., 2005. HPLC quantification of uncarine D and the antiplasmodial activity of alkaloids from leaves of Mitragyna inermis (Willd.) O. Kuntze. Phytochemical Analysis 16, 30–33.
François, G., Aké Assi, L., Holenz, J., Bringmann, G., 1996. Constituents of *Picralima nitida* display pronounced inhibitory activities against asexual erythrocytic forms of *Plasmodium falciparum in vitro*. Journal of Ethnopharmacology 54, 113–117.
Gertsch, J., 2009. How scientific is the science in ethnopharmacology? Historical perspectives and epistemological problems. Journal of Ethnopharmacology 122, 177–183.
Goffin, E., Ziemons, E., De Mol, P., de Ceu de Madureira, M., Martins, A.P., Proenca da Cunha, A., Philippe, G., Tits, M., Angenot, L., Frederich, M., 2002. *In vitro* antiplasmodial activity of *Tithonia diversifolia* and identification of its main active constituent: tagitinin C. Planta Medica 68, 543–545.
Guinovart, C., Aponte, J.J., Sacarlal, J., Aide, P., Leach, A., Bassat, Q., Macete, E., Dobaño, C., Lievens, M., Loucq, C., Ballou, W.R., Cohen, J., Alonso, P.L., 2009. Insights into long-lasting protection induced by RTS, S/AS02A malaria vaccine: further results from a phase IIb trial in Mozambican children. PLoS ONE 4, e5165.
Greenwood, B.M., Fidock, D.A., Kyle, D.E., Kappe, S.H.I., Alonso, P.L., Collins, F.H., Duffy, P.E., 2008. Malaria: progress, perils, and prospects for eradication. Journal of Clinical Investigation 118, 1266–1276.
Gomez, M.S., Piper, R.C., Hunsaker, L.A., Royer, R.E., Deck, L.M., Makler, M.T., Vander Jagt, D.L., 1997. Substrate and cofactor specificity and selective inhibition of lactate dehydrogenase from the malarial parasite *Plasmodium falciparum*. Molecular and Biochemical Parasitology 90, 235–246.
Haynes, R.K., 2001. Artemisinin and derivatives: the future for malaria treatment? Current Opinion in Infectious Diseases 14, 719–726.
Ibe, A.E., Nwufo, M.I., 2005. Identification, collection and domestication of medicinal plants in southeastern Nigeria. African Development 30, 66–77.
Igoli, J.O., Ogaji, O.G., Tor-Anyiin, T.A., Igoli, N.P., 2005. Traditional medicine practice amongst the Igede people of Nigeria. Part II. African Journal of Traditional Complementary and Alternative Medicine 2, 134–152.
Isah, A.B., Ibrahim, Y.K., Iwalewa, E.O., 2003. Evaluation of the antimalarial properties and standardization of tablets of *Azadirachta indica* (Meliaceae) in mice. Phytotherapy Research 17, 807–810.
Iwalewa, E.O., Lege-Oguntoye, L., Rai, P.P., Iyaniwura, T.T., Etkin, N.L., 1990. *In vitro* anti-malarial activity of leaf extracts of *Cassia occidentalis* and *Guiera senegalensis* in *Plasmodium yoelii nigeriensis*. West African Journal of Pharmaceutical and Drug Research 9, 19–21.
Iwalewa, E.O., Omisore, N.O., Adewunmi, C.O., Gbolade, A.A., Ademowo, O.G., Nneji, C., Agboola, O.I., Daniyan, O.M., 2008. Anti-protozoan activities of *Harungana madagascariensis* stem bark extract on trichomonads and malaria. Journal of Ethnopharmacology 117, 507–511.
Iwu, M.M., Obidoa, O., Anazodo, M., 1986. Biochemical mechanism of the antimalarial activity of *Azadirachta indica* leaf extract. Pharmacological Research Communications 18, 81–91.

Iwu, M.M., Klayman, D.L., 1992. Evaluation of the *in vitro* antimalarial activity of *Picralima nitida* extracts. Journal of Ethnopharmacology 36, 133–135.
Jones, I.W., Denholm, A.A., Ley, S.V., Lovell, H., Wood, A., Sinden, R.E., 1994. Sexual development of malaria parasites is inhibited in vitro by the neem extract azadirachtin, and its semi-synthetic analogues. FEMS Microbiology Letters 120, 267–273.
Joshi, S.P., Rojatkar, S.R., Nagasampagi, B.A., 1998. Antimalarial activity of neem (*Azadirachta indica*). Journal of Medicinal and Aromatic Plant Sciences 20, 1000–1004.
Kamanzi Atindehou, K., Schmid, C., Brun, R., Kone, M.W., Traore, D., 2004. Antitrypanosomal and antiplasmodial activity of medicinal plants from Côte d'Ivoire. Journal of Ethnopharmacology 90, 221–227.
Karou, D., Dicko, M.H., Sanon, S., Simpore, J., Traore, A.S., 2003. Antimalarial activity of *Sida acuta* Burm f. (Malvaceae) and *Pterocarpus erinaceus* Poir. (Fabaceae). Journal of Ethnopharmacology 89, 291–294.
Karou, D., Nadembega, W.M.C., Ilboudo, D.P., Ouermi, D., Gbeassor, M., De Souza, C., Simpore, J., 2007a. *Sida acuta* Burm. f.: a medicinal plant with numerous potencies. African Journal of Biotechnology 6, 2953–2959.
Karou, D., Nadembega, W.M.C., Ouattara, L., Ilboudo, D.P., Canini, A., Nikiéma, J.B., Simpore, J., Colizzi, V., Traore, A.S., 2007b. African Ethnopharmacology and New Drug Discovery. Medicinal and Aromatic Plant Science and Biotechnology 1, 1–7.
Kassim, O.O., Loyevsky, M., Elliott, B., Geall, A., Amonoo, H., Gordeuk, V.R., 2005. Effects of root extracts of *Fagara zanthoxyloides* on the *in vitro* growth and stage distribution of *Plasmodium falciparum*. Antimicrobial Agents and Chemotherapy 49, 264–268.
Kayode, J., 2006. Conservation of indigenous medicinal botanicals in Ekiti State, Nigeria. Journal of Zhejiang University Science B 7, 713–718.
Khalid, S.A., Friedrichsen, G.M., Kharazmi, A., Theander, T.G., Olsen, C.E., Christensen, S.B., 1998. Limonoids from *Khaya senegalensis*. Phytochemistry 49, 1769–1772.
Kimbi, H.K., Fagbenro-Beyioku, A.F., 1996. Efficacy of *Cymbopogon giganteus* and *Enantia chrantha* against chloroquine resistant *Plasmodium yoelii nigeriensis*. East African Medical Journal 73, 636–637.
Kirira, P.G., Rukunga, G.M., Wanyonyi, A.W., Muregi, F.M., Gathirwa, J.W., Muthaura, C.N., Omar, S.A., Tolo, F., Mungai, G.M., Ndiege, I.O., 2006. Anti-plasmodial activity and toxicity of extracts of plants used in traditional malaria therapy in Meru and Kilifi Districts of Kenya. Journal of Ethnopharmacology 106, 403–407.
Kitagawa, I., Mahmud, T., Yokota, Ko-ichi, Nakagawa, S., Mayumi, T., Kobayashi, M., Shibuya, H., 1996. Indonesian medicinal plants XVIII characterization of quassinoids from the stem of *Quassia indica*. Chemical and Pharmaceutical Bulletin 41, 2009–2014.
Kirby, G.C., Paine, A., Warhurst, D.C., Noamese, B.K., Phillipson, J.D., 1994. *In vitro* and *in vivo* antimalarial activity of cryptolepine, a plant-derived indoloquinoline. Phytotherapy Research 9, 359–363.
Klayman, D.L., 1985. *Qinghaosu* (artemisinin): an antimalarial drug from China. Science 228, 1049–1055.
Koumaglo, K., Gbeassor, M., Nikabu, O., deSouza, C., Werner, W., 1992. Effects of three compounds extracted from *Morinda lucida* on *Plasmodium falciparum*. Planta Medica 58, 533–534.
Krettli, A.U., 2009. Antimalarial drug discovery: screening of Brazilian medicinal plants and purified compounds. Expert Opinion in Drug Discovery 4, 95–108.
Krettli, A.U., Adebayo, J.O., Krettli, L.G., 2009. Testing of natural products and synthetic molecules aiming at new antimalarials. Current Drug Targets 10, 261–270.
Limmatvapirat, C., Sirisopanaporn, S., Kittakoop, P., 2004. Antitubercular and antiplasmodial constituents of *Abrus precatorius*. Planta Medica 70, 276–278.
MacKinnon, S., Durst, T., Arnason, J.T., Angerhofer, C., Pezutto, J., Sanchez-Vindas, P.E., Poveds, L.J., Gbeassor, M., 1997. Antimalarial activity of tropical Meliaceae extracts and gedunin derivatives. Journal of Natural Products 60, 336–341.
Majekodunmi, S.O., Adegoke, O.A., Odeku, O.A., 2008. Formulation of the extract of the stem bark of *Alstonia boonei* as tablet dosage form. Tropical Journal of Pharmaceutical Research 7, 987–994.
Makinde, J.M., Amusan, O.G., Adesogan, E.K., 1988. The antimalarial activity of *Spathodea campanulata* stem bark extract on *Ptasmodium berghei berghei* in mice. Planta Medica, Stuttgart 54, 122–125.
Makinde, J.M., Awe, S.O., Salako, L.A., 1994. Seasonal variation in the antimalarial activity of *Morinda lucida* on *Ptasmodium berghei* in mice. Fitoterapia 65, 124–130.
Makinde, J.M., Obih, P.O., Jimoh, A.A., 1987. Effect of *Solanum erianthum* aqueous leaf extract on *Ptasmodium berghei* in mice. African Journal of Medicine and Medical Science 16, 193–196.
Malomo, S.O., Adebayo, J.O., Olorunniji, F.J., 2001. Decrease in activities of cation ATPases and alkaline phosphatate in kidney and liver of artemether treatead rats. NISEB Journal 1, 175–182.
Masaba, S.C., 2000. The antimalarial activity of Vernonia amygdalina Del (compositae). Transaction of the Royal Society of Tropical Medicine and Hygiene 94, 694–695.
Menan, H., Banzouzi, J.T., Hocquette, A., Pelissier, Y., Blache, Y., Kone, M., Mallie, M., Assi, L.A., Valentin, A., 2006. Antiplasmodial activity and cytotoxicity of plants used in West African traditional medicine for the treatment of malaria. Journal of Ethnopharmacology 105, 131–136.
Mokuolu, O.A., Okoro, E.O., Ayetoro, S.O., Adewara, A.A., 2007. Effect of artemisinin-based treatment policy on consumption pattern of antimalarials. American Journal of Tropical Medicine and Hygiene 76, 7–11.
Morita, H., Oshimi, S., Hirasawa, Y., Koyama, K., Honda, T., Ekasari, W., Indrayanto, G., Zaini, N.C., 2007. Cassiarins A and B, novel antiplasmodial alkaloids from Cassia siamea. Organic Letters 9, 3691–3693.
Muhammad, S., Amusa, N.A., 2005. The important food crops and medicinal plants of North-western Nigeria. Research Journal of Agricultural and Biological Science 1, 254–260.
Ndjakou Lenta, B., Ngouela, S., Fekam Boyom, F., Tantangmo, F., Feuya Tchouya, G.R., Tsamo, E., Gut, J., Rosenthal, P.J., Donald Connolly, J., 2007. Anti-plasmodial activity of some constituents of the root bark of *Harungana madagascariensis* LAM. (Hypericaceae). Chemical and Pharmaceutical Bulletin (Tokyo) 55, 464–467.
Nundkumar, N., Ojewole, J.A., 2002. Studies on the antiplasmodial properties of some South African medicinal plants used as antimalarial remedies in Zulu folk medicine. Methods and Findings in Experimental and Clinical Pharmacology 24, 397–401.
Nwabuisi, C., 2002. Prophylactic effect of multi-herbal extract Agbo-Iba on malaria induced in mice. East African Medical Journal 79, 343–346.
Obih, P.O., Makinde, M., Laoye, O.J., 1985. Investigations of various extracts of *Morinda lucida* for antimalarial actions on *Plasmodium berghei berghei* in mice. African Journal of Medicine and Medical Science 14, 45–49.
Obih, P.O., Makinde, J.M., 1985. Effect of Azadirachta indica on Plasmodium berghei berghei in mice. African Journal of Medicine and Medical Science 14, 51–54.
Obute, G.C., 2005. Ethnomedicinal Plant Resources of South eastern Nigeria. Ethnobotanical Leaflets., http://www.siu.edu/~ebl/leaflets/obute.htm.
Odebiyi, O.O., Sofowora, E.S., 1979. Antimicrobial alkaloids from a Nigerian chewing stick (*Fagara zanthoxyloides*). Planta Medica 36, 204–207.
Odugbemi, T.O., Akinsulire, O.R., Aibinu, I.E., Fabeku, P.O., 2007. Medicinal plants useful for malaria therapy in Okeigbo, Ondo State, Southwest Nigeria. African Journal of Traditional Complementary and Alternative Medicine 4, 191–198.
Okokon, J.E., Antia, B.S., Igboasoiyi, A.C., Essien, E.E., Mbagwu, H.O., 2007a. Evaluation of antiplasmodial activity of ethanolic seed extract of *Picralima nitida*. Journal of Ethnopharmacology 111, 464–467.
Okokon, J.E., Ettebong, E., Antia, B.S., 2008. *In vivo* antimalarial activity of ethanolic extract of *Stachytarpheta cayennensis*. Indian Journal of Pharmacology 40, 111–113.
Okokon, J.E., Ita, B.N., Udokpoh, A.E., 2006a. The *in vivo* antimalarial activities of *Uvaria chamae* and *Hippocratea africana*. Annals of Tropical Medicine and Parasitology 100, 585–590.
Okokon, J.E., Ita, B.N., Udokpoh, A.E., 2006b. Antiplasmodial activity of *Cylicodiscus gabunensis*. Journal of Ethnopharmacology 107, 175–178.
Okokon, J.E., Ita, B., Udokpoh, A.E., 2006c. Antiplasmodial activity of *Homalium letestui*. Phytotherapy Research 20, 949–951.
Okokon, J.E., Udokpoh, A.E., Antia, B.S., 2007b. Antimalarial activity of ethanolic extract of *Tetrapleura tetraptera* fruit. Journal of Ethnopharmacology 111, 537–540.
Okokon, J.E., Ubulom, P.M., Udokpoh, A.E., 2007c. Antiplasmodial activity of *Setaria megaphylla*. Phytotherapy Research 21, 366–368.
Okpako, L.C., Ajaiyeoba, E.O., 2004. *In vitro* and *in vivo* antimalarial studies of *Striga hermothica* and *Tapinanthus sessilifolius* extracts. African Journal of Medicine and Medical Science 33, 73–75.
Okunji, C.O., Iwu, M.M., Ito, Y., Smith, P.L., 2005. Preparative separation of indole alkaloids from the rind of *Picralima nitida* (Stapf) T. Durand & H. Durand by pH-Zone-Refining Countercurrent chromatography. Journal of Liquid Chromatography and Related Technology 28, 775–783.
Onyeibor, O., Croft, S.L., Dodson, H.I., Feiz-Haddad, M., Kendrick, H., Millington, N.J., Parapini, S., Phillips, R.M., Seville, S., Shnyder, S.D., Taramelli, D., Wright, C.W., 2005. Synthesis of some cryptolepine analogues, assessment of their antimalarial and cytotoxic activities, and consideration of their antimalarial mode of action. Journal of Medicinal Chemistry 48, 2701–2709.
Oshimi, S., Tomizawa, Y., Hirasawa, Y., Honda, T., Ekasari, W., Widyawaruyanti, A., Rudyanto, M., Indrayanto, G., Zaini, N.C., Morita, H., 2008. Chrobisiamone A, a new bischromone from Cassia siamea and a biomimetic transformation of 5-acetonyl-7-hydroxy-2-methylchromone into cassiarin A. Bioorganic and Medicinal Chemistry Letters 18, 3761–3763.
Perez, H.A., De La Rosa, M., Apitz, R., 1994. *In vivo* activity of ajoene against rodent malaria. Antimicrobial Agents Chemotherapy 38, 337–339.
Peters, W., 1965. Drug resistance in *Plasmodium berghei* Venke and Lips (1948). I. Chloroquine resistance. Experimental Parasitology 17, 80–87.
Phillipson, J.D., Wright, C.W., 1991. Can ethnopharmacology contribute to the development of antimalarial agents? Journal of Ethnopharmacology 32, 155–171.
Royer, R.E., Deck, L.M., Campos, N.M., Hunsaker, L.A., Vander Jagt, D.L., 1986. Biologically active derivates of gossypol: synthesis and antimalarial activities of peri-acylated gossylic nitriles. Journal of Medicinal Chemistry 29, 1799–1801.
Ryley, J.F., Peters, W., 1970. The antimalarial activity of some quinone esters. Annals of Tropical Medicine and Parasitology 84, 209–222.
Saidu, K., Onah, J., Orisadipe, A., Olusola, A., Wambebe, C., Gamaniel, K., 2000. Antiplasmodial, analgesic, and anti-inflammatory activities of the aqueous extract of the stem bark of *Erythrina senegalensis*. Journal of Ethnopharmacology 71, 275–280.
Sanon, S., Ollivier, E., Azas, N., Mahiou, V., Gasquet, M., Ouattara, C.T., Nebie, I., Traore, A.S., Esposito, F., Balansard, G., Timon-David, P., Fumoux, F., 2003. Ethnobotanical survey and in vitro antiplasmodial activity of plants used in traditional medicine in Burkina Faso. Journal of Ethnopharmacology 86, 143–147.
Saxena, S., Pant, N., Jain, D.C., Bhakuni, R.S., 2003. Antimalarial agents from plant sources. Current Science 85, 1314–1329.
Shuaibu, M.N., Wuyep, P.A., Yanagi, T., Hirayama, K., Tanaka, T., Kouno, I., 2008. The use of microfluorometric method for activity-guided isolation of antiplasmodial compound from plant extracts. Parasitology Research 102, 1119–1127.

Sittie, A.A., Lemmich, E., Olsen, C.E., Hviid, L., Kharazmi, A., Nkrumah, F.K., Christensen, S.B., 1999. Structure–activity studies: in vitro antileishmanial and antimalarial activities of anthraquinones from *Morinda lucida*. Planta Medica 65, 259–261.

Snow, R.W., Guerra, C.A., Noor, A.M., Myint, H.Y., Hay, S.I., 2005. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. Nature 434, 214–217.

Spencer, C.F., Koniuszy, F.R., Rogers, E.F., Shavel, J., Easton, N.R., Kaczka, E.A., Kuehl, F.A., Phillips, R.F., Walti, A., Folkers, K., 1947. Survey of plants for antimalarial activity. Lloydia 10, 145–174.

Steele, J.C.P., Warhurst, D.C., Kirby, G.C., Simmonds, M.S.J., 1999. In vitro and in vivo evaluation of betulinic acid as an antimalarial. Phytotherapy Research 13, 115–119.

Tchoumbougnang, F., Zollo, P.H., Dagne, E., Mekonnen, Y., 2005. In vivo antimalarial activity of essential oils from *Cymbopogon citratus* and *Ocimum gratissimum* on mice infected with *Plasmodium berghei*. Planta Medica 71, 20–23.

Tona, L., Cimanga, R.K., Mesia, K., Musuamba, C.T., De Bruyne, T., Apers, S., Hernans, N., Van Miert, S., Pieters, L., Totté, J., Vlietinck, A.J., 2004. *In vitro* antiplasmodial activity of extracts and fractions from seven medicinal plants used in the Democratic Republic of Congo. Journal of Ethnopharmacology 93, 27–32.

Tor-Anyiin, T.A., Shaato, R., Oluma, H.O.A., 2003. Ethnobotanical survey of antimalarial medicinal plants amongst the Tiv people of Nigeria. Journal of Herbs, Spices and Medicinal Plants 10, 61–74.

Trager, W., Jensen, J.B., 1976. Human malaria parasites in continuous culture. Science 193, 673–675.

Tona, L., Ngimbi, N.P., Tsakala, M., Mesia, K., Cimanga, K., Apers, S., De Bruyne, T., Pieters, L., Totte, J., Vlietinck, A.J., 1999. Antimalarial activity of 20 crude extracts from nine African medicinal plants used in Kinshasa, Congo. Journal of Ethnopharmacology 68, 193–203.

Valentin, A., Pélissier, Y., Benoit, F., Marion, C., Kone, D., Mallie, M., Bastide, J.M., Bessière, J.M., 1995. Composition and antimalarial activity in vitro of volatile components of *Lippia multiflora*. Phytochemistry 40, 1439–1442.

Vonthron-Senecheau, C., Weniger, B., Ouattara, M., Bi, F.T., Kamenan, A., Lobstein, A., Brun, R., Anton, R., 2003. In vitro antiplasmodial activity and cytotoxicity of ethnobotanically selected Ivorian plants. Journal of Ethnopharmacology 87, 221–225.

Waako, P.J., Katuura, E., Smith, P., Folb, P., 2007. East African medicinal plants as a source of lead compounds for the development of new antimalarial drugs. African Journal of Ecology 45, 102–106.

WHO, 2008a. World Malaria Report 2008. World Health Organization, Geneva, pp. 7–15, 99–101.

WHO, 2008b. Global Burden of Disease: 2004 Update. World Health Organization, Geneva, http://www.who.int/healthinfo/bodestimates/en/index.html.

Willcox, M.L., 1999. A Clinical trial of 'AM', a Ugandan herbal remedy for malaria. Journal of Public Health Medicine 21, 318–324.

Willcox, M.L., Bodeker, G., 2004. Traditional herbal medicines for malaria. British Medical Journal 329, 1156–1159.

Zirihi, G.N., Mambu, L., Guédé-Guina, F., Bodo, B., Grellier, P., 2005. *In vitro* antiplasmodial activity and cytotoxicity of 33 West African plants used for treatment of malaria. Journal of Ethnopharmacology 98, 281–285.