The potential of anti-malarial compounds derived from African medicinal plants, part II: a pharmacological evaluation of non-alkaloids and non-terpenoids

Fidele Ntie-Kang1,2†, Pascal Amoa Onguéné3†, Lydia L Lifongo1, Jean Claude Ndom3, Wolfgang Sippl2 and Luc Meva’a Mbaze3*

Abstract
Malaria is currently a public health concern in many countries in the world due to various factors which are not yet under check. Drug discovery projects targeting malaria often resort to natural sources in the search for lead compounds. A survey of the literature has led to a summary of the major findings regarding plant-derived compounds from African flora, which have shown anti-malarial/antiplasmodial activities, tested by in vitro and in vivo assays. Considerations have been given to compounds with activities ranging from “very active” to “weakly active”, leading to >500 chemical structures, mainly alkaloids, terpenoids, flavonoids, coumarins, phenolics, polyacetylenes, xanthones, quinones, steroids and lignans. However, only the compounds that showed anti-malarial activity, from “very active” to “moderately active”, are discussed in this review.

Keywords: Africa, Malaria, Medicinal plants, Natural products, Traditional medicine

Background
Malaria is caused by protozoans of the genus Plasmodium (Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, and Plasmodium vivax) [1,2]. According to the World Health Organization (WHO), about half of the world’s population is at risk of malaria and one to two million annual deaths (mostly among African children) can be attributed to malaria alone [3,4]. The causative agent is transmitted by the female Anopheles mosquito species, which has also developed resistance against insecticides, such as dichlorodiphenyltrichloroethane (DDT), and chemoprophylaxis has not often yielded the expected results [2]. Additionally, the disease-causing protozoans have developed resistance against most of the drugs currently used to treat malaria. There is an urgent need to discover new active compounds.

Nature, and particularly plants are a potential source of new anti-malarial drugs, since they contain a quantity of metabolites with a great variety of structures and pharmacological activities. Traditional preparations (with the use of macerations, extracts, steam baths, concoctions, and decoctions from plant materials) have been the main source of treatment of malaria in Africa [5] and other continents where the disease is endemic [6,7]. Thus, with failing treatment regimens, many research groups in Africa (African indigenous research groups and their foreign collaborators) have resorted to plant sources in the quest to expand the anti-malarial chemotherapeutic arsenal [1,8,9]. This effort has been motivated by the use of these plant materials in the treatment of malaria and fevers in African traditional medicine (ATM). The results from Africa and other continents have been quite promising and hence there has been a general call for the use of natural products as drugs or as sources of inspiration for the development of novel anti-malarials, in order to possibly avoid problems related to drug resistance [10-12].

* Correspondence: lmbaze@yahoo.fr
†Equal contributors
3Department of Chemistry, Faculty of Science, University of Douala, PO Box 24157, Douala, Cameroon
Full list of author information is available at the end of the article

© 2014 Ntie-Kang et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
It is believed that the next generation anti-malarials or the scaffolds necessary for their synthesis may be found in the plants currently used in ATM [13,14]. However, the last review on anti-malarial compounds from African flora dates back about ten years [13], with other reviews focusing on plant-screening campaigns in particular regions and/or countries in Africa [15-35] or on active compounds obtained by bioassay-guided fractionation efforts from given countries and/or regions, not covering an entire continent [36-41]. Even though natural products that are active against *P. falciparum* have been discussed in a number of review papers [1,42-48], the goal has been to provide an coverage of the most promising anti-malarials from the entire African continent, by giving an overview of the most pertinent *in vitro* and *in vivo* screening results reported in the literature. The most successful anti-malarials in use to date have been derived from natural product sources (quinolones/artemisinins). It is indeed a glaring omission that the African continent, despite its rich ethno-pharmacological heritage, is yet to yield a significant contribution in this respect. Clearly, as a first step, a systematic review of the many traditional therapeutic options is needed and this review addresses an important issue in this aspect. In part I, the most promising alkaloids and terpenoids were presented [49], while in this part the most interesting findings for flavonoids, coumarins, phenolics, polyacetylenes obtained by bioassay-guided fractionation efforts from given countries and/or regions, not covering an entire continent [36-41]. Even though natural products that are active against *P. falciparum* have been discussed in a number of review papers [1,42-48], the goal has been to provide an coverage of the most promising anti-malarials from the entire African continent, by giving an overview of the most pertinent *in vitro* and *in vivo* screening results reported in the literature. The most successful anti-malarials in use to date have been derived from natural product sources (quinolones/artemisinins). It is indeed a glaring omission that the African continent, despite its rich ethno-pharmacological heritage, is yet to yield a significant contribution in this respect. Clearly, as a first step, a systematic review of the many traditional therapeutic options is needed and this review addresses an important issue in this aspect. In part I, the most promising alkaloids and terpenoids were presented [49], while in this part the most interesting findings for flavonoids, coumarins, phenolics, polyacetylenes, xanthenes, quinones, steroids, and lignans are shown. The last part of the work is essentially on the cheminformatic analysis of >500 natural products (NPs), derived from African medicinal plants, which have demonstrated from weak to very good *in vitro* anti-malarial activities, with a focus on molecular descriptors related to “drug-likeness”, drug metabolism and pharmacokinetics (DMPK). The predicted properties of plant-derived anti-malarials are those related to drug absorption, distribution, metabolism, elimination, and toxicity (ADMET) based on *in silico* computed molecular descriptors.

### Promising anti-malarial agents derived from African flora

By convention, activities were categorised into “very potent”, “good”, “good to moderate”, “weak”, “very weak” and “inactive”. Following criteria used by Mahmoudi *et al.* [50] and Wilcox *et al.* [51], a pure compound was considered highly active if IC$_{50}$ < 0.06 μM, being active with 0.06 μM ≤ IC$_{50}$ ≤ 5 μM, weakly active when 5 μM ≤ IC$_{50}$ ≤ 10 μM and compounds with IC$_{50}$ > 10 μM were considered inactive. The following inhibition percentages were proposed for *in vivo* activity of antimalarial extracts at a fixed dose of 250 mg kg$^{-1}$ day$^{-1}$: 90-100% (very good activity); 90-50% (good to moderate); 50-10% (moderate to weak); 0% (inactive) [52].

### Flavonoids

Several bioactive flavonoids have been derived from medicinal plants growing in Africa. Even though the molecular mechanism of action of anti-malarial activities of flavonoids is not fully elucidated, it is believed that flavonoids act by inhibiting the fatty acid biosynthesis (FAS II) of the parasite [53,54]. Some flavonoids have also been shown to inhibit the influx of L-glutamine and myo-inositol into infected erythrocytes [55]. The active anti-malarial flavonoids are summarized in Table 1, while the chemical structures are shown in Figures 1, 2 and 3.

### Chalcones

Several anti-malarial flavonoids have been isolated from the stem bark of *Erythrina abyssinica* by Yenesew *et al.* [56,57]. These include chalcones, prenylated and non-prenylated isoflavones and flavones, pterocarpenes, and flavenes. All compounds exhibited moderate anti-malarial activity against the D6 and W2 strains of *P. falciparum*. The ethyl acetate extract of the stem bark of this plant showed anti-plasmodial activity against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum* with IC$_{50}$ values of 7.9 and 5.3 μg mL$^{-1}$, respectively. From this extract, a new chalcone, 2′,3,4,4′-tetrahydroxy-5-prenylchalcone or 5-prenylbutein (1), a new flavanone, 4′,7-dihydroxy-3′-methoxy-5′-prenyllavbane (trivial name, 5-deoxyxybassinin II) and homobutein (2), along with known flavonoids have been isolated as the antiplasmodial principles. Yenesew *et al.* also investigated the stem bark of *Milletia usaramensis* ssp. *usaramensis* (Leguminosae) from Kenya [58]. The chalcone 4′-O-galangylisoquiritigenin (3) was isolated. This compound exhibited moderate to weak anti-plasmodial activity against the D6 and W2 strains of *P. falciparum*. Nkunya *et al.* investigated several Tanzanian species of the genus *Uvaria* [59]. Petroleum ether, dichloromethane and methanol extracts of leaves, stem, and root bark of nine *Uvaria* species: *Uvaria dependens*, *Uvaria faulknerae*, *Uvaria kirkii*, *Uvaria leptoclodon*, *Uvaria lucida* ssp. *lucida*, *Uvaria* sp. (Pande), *Uvaria scheffleri*, and *Uvaria tanzanicae* were tested for their *in vitro* activity against the multidrug-resistant K-1 strain of *P. falciparum*. The IC$_{50}$ values of the extracts varied between 5 and 500 μg mL$^{-1}$. The most active extracts were obtained from the stem and root bark of *U. lucida* ssp. *lucida* and *Uvaria* sp. (Pande) and the root bark of *U. scheffleri*, all of which had IC$_{50}$ values between 5 and 9 μg mL$^{-1}$. The investigations of these authors yielded five important chalcones, uvaretin (4), diuvaretin (5), triuvaretin, isotriuvaretin and chamuvaretin (6). These compounds showed moderate to high antiplasmodial activity against the multidrug-resistant K-1 strain of *P. falciparum*, with respective IC$_{50}$ values of 3.49, 4.20, 46.02, 20.85 and 5.32 μg mL$^{-1}$. Joseph *et al.* also isolated two
| Compound subclass | Isolated metabolites | Plant species (Family) | Part of plant studied | Place of harvest (locality, country) | Author, reference |
|-------------------|----------------------|------------------------|-----------------------|--------------------------------------|------------------|
| Chalcones         | 1 and 2              | *Erythrina abyssinica* (Leguminosae) | Stem bark            | Thika town, Kenya                    | Yenesew et al. [56,57] |
|                   | 3                    | *Millettia usaramensis* ssp. *usaramensis* (Leguminosae) | Stem bark            | Jadini Forest, Kenya                 | Yenesew et al. [58] |
|                   | 4, 5 and 6           | *Uvaria* sp. (Annonaceae) | Leaves, stem and root bark | Tanzania                            | Nkunya et al. [59] |
|                   | 7 and 8              | *Friesodielsia obovata* (Annonaceae) | Root bark            | Tabora district, Tanzania            | Joseph et al. [60] |
|                   | 9, 10, 11, 12, 13, and 14 | *Polygonum senegalense* (Polygonaceae) | Aerial parts            | Nairobi, Kenya                        | Midowo et al. [61] |
|                   | 4 and 15             | *Uvaria puguensis* (Annonaceae) | Stem bark            | Pugu Forest Reserve, Tanzania        | Makangara et al. [62] |
|                   | 16, 17, 18, and 19   | *Dorstenia barteri* (Moraceae) | Twigs                | Tombel, Cameroon                      | Ngameni et al. [63] |
| Flavonones        | 20, 21, 22, 23, 24, and 25 | *Erythrina abyssinica* (Leguminosae) | Stem bark            | Thika town, Kenya                    | Yenesew et al. [56,57] |
|                   | 26 and 27            | *Derris trifoliata* (Leguminosae) | Seed pods            | Coast Province, Kenya                 | Yenesew et al. [64] |
|                   | 28 and 29            | *Polygonum senegalense* (Polygonaceae) | Aerial parts            | Nairobi, Kenya                        | Midowo et al. [61] |
|                   | 30                   | *Erythrina abyssinica* (Leguminosae) | Stem bark            | Thika town, Kenya                    | Yenesew et al. [57] |
|                   | 31 and 32            | *Morus mesozygia* (Moraceae) | Stem bark            | Centre Province, Cameroon            | Zelefack et al. [65] |
| Isoflavones       | 33                   | *Ficus mucuso* (Moraceae) | Figs                  | Tongolo-Yaoundé, Cameroon            | Bankeu et al. [66] |
|                   | 34                   | *Erythrina sacleuxii* (Leguminosae) | Root bark            | Kenya                                | Andayi et al. [67] |
| Retinoids         | 35, 36, 37 and 38    | *Millettia usaramensis* ssp. *usaramensis* (Leguminosae) | Stem bark            | Jadini Forest, Kenya                 | Yenesew et al. [58] |
bioactive chalcones; 3′,5′-diformyl-2′,4′,6′-trihydroxychalcone (7) and 3′,5′-dimethyl-2′,4′,6′-trihydroxychalcone (8) from the root bark of *Friesodielsia obovata* [60]. These two compounds exhibited moderate antiplasmodial activity against the K-1 strain of *P. falciparum*, with respective IC\textsubscript{50} values of 23 and 9.7 μg L\textsuperscript{−1}. The same trend of activity was observed against the NF54 strain, against which the compounds had IC\textsubscript{50} values of 29 and 8.5 μg L\textsuperscript{−1} respectively.

The new homoisoflavonoid, 5,7-dihydroxy-3-(hydroxyphenyl-methyl)-6-methoxy-chroman-4-one or polygohomoisoflavanone (9) was isolated from the aerial exudates of *Polygonum senegalense*, along with the known chalcones 10 to 14, by Midowo *et al.* [61]. The new compound, along with other components of the aerial exudate showed good antimalarial activities towards D6 and W2 strains of *P. falciparum*. Mukaranga *et al.* investigated the stem bark of *Uvaria puguensis* (Annonaceae) from Tanzania [62]. Repeated chromatography of the petroleum ether and chloroform extracts yielded uvaretin (4) and the new phenanthrenoid 6-hydroxy-3-methoxy-4-oxaapyren-5-one (15), which has been named puguenolide.

The chalcones bartericin A (16), and 4-hydroxylonchocarpin (17), stipulin (18) and kanzonol B (19) were isolated from the twigs of *Dorstenia barteri* (Moraceae) from Cameroon by Ngameni *et al.* [63]. These compounds were evaluated in culture against the W2 strain
of *P. falciparum*. The evaluated compounds were found to be active *in vitro* against *P. falciparum*, demonstrating particular potencies with relatively low IC_{50} values (2.15 μM, 3.36 μM and 5.13 μM respectively). The observed activities confirmed the chalcones as potential leads for the development of anti-malarials.

**Flavanones**

The flavanones 5-deoxyabyssinin II (20), abyssinone IV (21), abyssinone V (22), sigmoidins A (23), B (24) and E (25), as well as 5-deoxyabyssinin II (30) were isolated from the stem bark of *Erythrina abyssinica* (Leguminosae), harvested in Kenya [57]. The investigations of Yenesew *et al.* demonstrated that these compounds exhibited anti-malarial properties against the W2 and D6 strains of *P. falciparum* with IC_{50} values varying from 4.9 to 13.6 μM against the latter strain and from 5.9 to 13.3 μM against the former strain [56,57]. The same authors investigated the seed pods of *Derris trifoliata* (Leguminosae) [64]. From the dichloromethane-methanol (1:1) extract, a new flavanone derivative (S)-lupinifolin 4′-methyl ether (26) was isolated, in addition to the known flavonoids lupinifolin (27) and rotenone. Lupinfolin only showed moderate *in vitro* antiplasmodial activity against the D6 and W2 strains of *P. falciparum*. The different parts of this plant showed larvicidal activities against *Aedes aegypti* and rotenoids were identified as the active principles [64]. Midowo *et al.* examined the aerial exudates of *Polygonum senegalense*
and reported the isolation, characterization and antiplasmodial activities of the first 9-hydroxyhomoisoflavonoid (28), 2,3-dihydro-5-hydroxy-7-methoxy-2-phenylchromen-4-one (29), along with the antiplasmodial activities of some of chalconoids and a flavanone isolated along with it from the surface exudate of *Polygonum senegalense* [61].

The antiplasmodial and cytotoxic activities of flavonoids and arylbenzofuran derivatives from *Morus mesozygia* were investigated by Zelefack et al. [65]. This plant is used in treating many diseases, including malaria and fever. Fractionation of the methanolic extract of its stem bark led to the isolation and identification of two flavonoids: artocarpesin (31) and kushenol E (32), among other compounds (mulberrofuran F, bartericin A and 4-hydroxylonchocarpin). The methanolic extract and the isolated compounds were tested for antiplasmodial activity against the chloroquine-resistant FcB1 *P. falciparum* strain and cytotoxicity on MCF-7 human breast cancer cells. It was found that all compounds were active against the FcB1 strain of *Plasmodium*, with compounds 31, 32 and mulberrofuran F exhibiting particular potency (with the median inhibitory concentrations IC50 = 2.5-2.6 μg mL⁻¹).

### Isoflavones

The isoflavone dimer, mucusisoflavone C (33), derived from the figs of *Ficus mucuso*, harvested near Yaoundé in Cameroon, exhibited a weak inhibitory activity against the validated drug target *P. falciparum* enol-ACP reductase (PfENR), with an IC50 value of 7.69 μM [66].

The acetone extracts of the root bark and stem bark of *Erythrina sacleuxii* showed antimalarial activities against the D6 and W2 strains of *P. falciparum*. Further chromatographic separation of the acetone extract of the root bark by Andayi et al. afforded a new isoflavone, 7-hydroxy-4′-methoxy-3′-prenylisoflavone, named 5-deoxy-3′-prenylbiochanin A (34) along with known isoflavonoids as the antiplasmodial principles [67]. Flavonoids and isoflavonoids isolated from the stem bark of *E. sacleuxii* were also tested and showed antiplasmodial activities.

### Rotenoids

*Milletia usaramensis* ssp. *usaramensis* is a plant growing in East Africa, which is reported to contain anti-malarial flavonoids, particularly rotenoids [58]. Seven rotenoids have been reported from this species, including usararotenoid C (35), usararotenoid A (36), (+)-usararotenoid B (37), and (+)-12α-epi-millettosin (38). These compounds exhibited moderate to weak antiplasmodial activity against the D6 and W2 strains of *P. falciparum*. Yenesew et al. further established some structure–activity relationships. It was observed that rotenoids containing a prenyl unit or a 2,2-dimethylpyrano substituent were more potent than the non-prenylated rotenoid, e.g., usararotenoid A. It was also reported that there is no significant activity for usararotenoid B, suggesting the importance of the carbonyl function at C-12 in usararotenoid A for the weak antiplasmodial activity observed.

### Phenolics

Zofou et al. have isolated *p*-hydroxy-cinnamic acid (39), along with other compounds, atranorin, specicoside, 2β,3β,19α-trihydroxy-urs-12-20-en-28-oic acid, from the stem bark of *Kigelia africana* (Bignoniaceae), harvested from Cameroon and performed the drug interactions of the isolated compounds among themselves, as well as their combination effects with quinine and artemether [68]. The antiplasmodial activity and drug interactions were evaluated against the multidrug-resistant W2mef

![Figure 3 Promising anti-malarial retenoids from African medicinal plants.](http://www.malariajournal.com/content/13/1/81)
Table 2 Summary of promising anti-malarial phenolics, polyacetylenes and quinones derived from African flora

| Compound class | Isolated metabolites | Plant species (Family) | Part of plant studied | Place of harvest (locality, country) | Author, reference |
|----------------|----------------------|------------------------|----------------------|--------------------------------------|-------------------|
| Phenolics      |                      |                        |                      |                                      |                   |
| 39             | Kigelia africana     | Stem bark              | Bandjoun, Cameroon    | Zofou et al. [68,69]                 |                   |
| 40 and 41      | Sorindeia juglandifolia | Fruits                | Mt. Kalla, Yaoundé, Cameroon | Boyom et al. [70]                   |                   |
|                |                      |                        |                      | Kamkumo et al. [71]                  |                   |
| 42             | Combretum molle      | Stem bark              | Tigray region, Northern Ethiopia | Asres et al. [72]                   |                   |
| 43             | Alchornea cordifolia | Leaves                 | Ivory Coast          | Banzouzi et al. [73]                 |                   |
| 44             | Vepris uguensis      | Roots                  | Baringo District, Kenya | Cheplogó et al. [74]                 |                   |
| 45             | Garcinia polyantha   | Roots                  | Mt Kalla, Yaoundé, Cameroon | Lannang et al. [75]                 |                   |
| 46             | Gossypium sp.        | Seeds                  | Diverse regions from the continent | Deck et al. [76]                    |                   |
| Polyacetylenes | 47, 48, 49 and 50   | Cussonia zimmermanii   | Root bark            | Senn et al. [77]                     |                   |
| Quinones       | 51, 52, 53 and 54   | Hoslunda opposita      | Root bark            | Achenbach et al. [78]                |                   |
|                | 55                   | Cassia siamea          | Stem bark            | Otu (Oyo State), Nigeria             | Ajayeoba et al. [79] |
|                | 56, 57, 58, 59, 60 and 61 | Psorospermum glabenum (Hypericaceae) | Root bark           | Ekombité, Cameroon                  | Lenta et al. [80] |
|                | 62, 63, 64, 65 and 66 | Harungana madagascariensis (Hypericaceae) | Root bark           | Bazou, Cameroon                     | Lenta et al. [81] |
|                | 67                   | Spathodea campanulata  | Stem bark            | Ibadan, Nigeria                     | Makinde et al. [82] |
|                | 68 and 69            | Kniphofia foliosa      | Roots                |                                      | Dagne et al. [83] |
|                |                      |                        |                      |                                      | Bringmann et al. [84] |
|                | 70 and 71            | Kigelia pinnata        | Root bark            | Weiss et al. [85]                   |                   |
strain of *P. falciparum*. The results equally showed a slight synergistic effect between atranorin and 2β,3β,19α-trihydroxy-urs-12-20-en-28-oic acid (combination index, CI of 0.82) whereas the interaction between specioside and *p*-hydroxycinnamic acid was instead antagonistic (CI of 2.67). All three compounds were shown to significantly act in synergy with some first line malaria drugs like artemether (CI of 0.42 to 0.71). More excitingly, none of these four compounds showed any significant sign of toxicity against the monkey kidney cell strains LLC-MK2 (selectivity index below 10). Compound 39 exhibited antiplasmodial activity against the W2mef strain with an IC$_{50}$ value of 2.11 μg mL$^{-1}$ [69].

The origins of the isolated anti-malarial/antiplasmodial phenolics are shown in Table 2, while the chemical structures are shown in Figure 4.

In an effort to identify a lead compound for anti-malarial drug discovery, Kamkumo *et al.* investigated the

---

**Figure 4** Promising anti-malarial/antiplasmodial phenolics from African medicinal plants.

8-hydroxyheptadeca-4,6-diyne-3-yl acetate (47)

8-hydroxyheptadeca-1-ene-4,6-diyne-3-yl acetate (48)

16-acetoxy-11-hydroxoctadeca-17-ene-12,14-diyneyl acetate (49)

11,16-diacetoxyoctadeca-17-ene-12,14-diyneyl acetate (50)
fruits of Sorindeia juglandifolia (Anacardiaceae) from Mt Kalla in Cameroon and tested the isolated compounds in vitro against the P. falciparum W2, against field isolates of P. falciparum, and against the P. falciparum recombinant cysteine protease falcipain-2 [70,71]. The main end products of the activity-guided fractionation were 2,3,6-trihydroxy benzoic acid (40) and 2,3,6-trihydroxy methyl benzoate (41). Overall, nine fractions tested against P. falciparum W2 and falcipain-2 were active, with IC_{50} values of varying from 2.3 to 11.6 μg mL^{-1} for W2, and 1.1-21.9 μg mL^{-1} for falcipain-2. Purified compounds (40 and 41) also showed inhibitory effects against P. falciparum W2 (IC_{50} 16.5 μM and 13.0 μM) and falcipain-2 (IC_{50} 35.4 and 6.1 μM). In studies of P. falciparum isolates from Cameroon, the plant fractions demonstrated IC_{50} values of 0.14-19.4 μg mL^{-1} and compounds (40 and 41) values of 6.3 and 36.1 μM. In vivo assessment of compound 40 showed activity against Plasmodium berghei strain B, with mean parasitaemia suppressive dose and curative dose of 44.9 mg kg^{-1} and...

Figure 6 Anti-malarial/antiplasmodial quinones from African medicinal plants.
42.2 mg kg\(^{-1}\), respectively. Active fractions were found to be safe in mice after oral administration of 7 g kg\(^{-1}\) body weight. These results suggest that further investigation of the anti-malarial activities of natural products from \textit{S. juglandifolia} will be appropriate.

The Ethiopian medicinal plant \textit{Combretum molle} (Combretaceae), reported to possess genuine anti-malarial activity, was investigated by Asres et al. [72]. The fractionation of the stem bark extract yielded punicalagin (42) as the active compound. This compound exhibited \textit{in vitro} anti-malarial activity against the 3D7 strain of \textit{P. falciparum} with IC\(_{50}\) values of 2.19 \(\mu\)g mL\(^{-1}\). Ellagic acid (43), derived from the leaves of \textit{Alchornea cordifolia} (Euphorbiaceae), showed good activity against \textit{P. berghei} in mice with an ED\(_{50}\) in the range of 0.2-0.151 \(\mu\)g mL\(^{-1}\) [73]. Cheplogoi et al. investigated the roots of \textit{Vepris uguenensis} (Rutaceae), harvested from the Baringo District, Kenya [74]. Syringaldehyde (44) was identified as an active compound, exhibiting moderate antiplasmodial activity against two strains of \textit{P. falciparum}, with IC\(_{50}\) values of 13.0 \(\mu\)g mL\(^{-1}\) (chloroquine-resistant 3D7 strain) and 21.4 \(\mu\)g mL\(^{-1}\) (chloroquine-resistant FCM29 strain), respectively.

From the methanol extract of roots of \textit{Garcinia polyantha}, Lannang et al. isolated Isoxanthochymol (45), which exhibited \textit{in vitro} anti-malarial activity against \textit{P. falciparum} and showed strong chemosuppression of parasitic growth [75]. The compound exhibited anti-malarial activity with an IC\(_{50}\) of 2.21 \(\mu\)M. This was lower than the IC\(_{50}\) of the other five co-occurring compounds (garcinane, smeathxanthones A and B, chefoxanthone, isoaxanthochymol, magnificol, and \(\beta\)-sitosterol and garcinixanthone I), which ranged from 2.5 to 4.1 \(\mu\)M. The compounds were administered over a period of four days to the culture and the number of parasites was determined daily. Control experiments were performed either without treatment or with administration of 0.032 \(\mu\)M chloroquine in the same solvent. Gossypol (46), derived from the seeds of cotton plant (\textit{Gossypium} sp., Malvaceae), exhibits a variety of biological activities, including antispermatogenic, anti-cancer, antiparasitic and antiviral activity. Deck et al. demonstrated that this compound also showed anti-malarial activity against both chloroquine-sensitive and chloroquine-resistant strains of \textit{P. falciparum}, with IC\(_{50}\) values in the order of 10 \(\mu\)M [76]. The presence of aldehyde functional groups renders gossypol toxic and in the light of this fact, authors further investigated synthetic analogues of compound 46 for biological activity. It was found that the synthetic analogues lost toxicity while retaining antiplasmodial activity.

**Polycyetylenes**

Polycyetylenes have unique chemical structures, which make them rare and often unstable and very reactive. They thus have a wide variety of biochemical and pharmacological uses. Senn et al. investigated the root bark extract of \textit{Cussonia zimmermanii} (Araliaceae) from the Pugu Forest in Tanzania, a plant commonly used to

---

**Table 3 Summary of promising anti-malarial coumarins and xanthone derived from African flora**

| Compound class | Isolated metabolites | Plant species (Family) | Part of plant studied | Place of harvest (City, Country) | Author, Reference |
|----------------|----------------------|------------------------|-----------------------|---------------------------------|-------------------|
| Coumarins      | 72 and 73            | Vemonia brachylyca (Asteraceae) | Roots                | Rachuonyo District, Kenya        | Cubukcu et al. [86] |
|                | 74                   | Tododia asiatica (Rutaceae)   | Roots                |                                  | Oketcho-Rabah et al. [88] |
|                | 75                   | Schefflera umbellifera (Araliaceae) | Leaves               | Limpopo, South Africa           | Mthembu et al. [89] |
| Xanthones      | 76 and 77            | Hypericum lanceolatum (Hypericaceae) | Stem bark           | Mt. Bamboutsos, Cameroon         | Zofou et al. [90] |
|                | 78, 79, 80, 81, 82 and 83 | Allantblackia monticola (Guttiferae) | Stem bark          | Bagangté, Cameroon               | Azebaze et al. [91] |
|                | 84, 85 and 86        | Symphonnia globulifera (Clusiaceae) | Seeds              | Fundong, Cameroon                | Ngouela et al. [92] |
|                | 87, 88, 89 and 90    | Pentadesma butyacea (Guttiferae) | Fruit pericarp      | Bazou, Cameroon                  | Lenta et al. [93] |

---

**Figure 7 Coumarins from from African medicinal plants with promising anti-malarial/antiplasmodial activities.**

---
treat malaria, fever and epilepsy [77]. Four polyacetylenes were isolated, namely: 8-hydroxyheptadeca-4,6-diyn-3-yl acetate (47), 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate (48), 16-acetoxy-11-hydroxyoctadeca-17-ene-12,14-diynyl acetate (49) and 11,16-diacetoxyoctadeca-17-ene-12,14-diynyl acetate (50), Figure 5. Compounds 47 to 49 showed high anti-malarial activity against \textit{P. falciparum}, with IC$_{50}$ values of 5.9, 0.44 and 0.84 μM respectively.

**Quinones**

Quinones also exhibit diverse pharmacological properties, including anti-malarial activity. Four quinones have been isolated from the root bark of \textit{Hoslundia opposita} by Achenbach \textit{et al.} [78], including 3-\textit{O}-benzoylhosloppone (51), 3-\textit{O}-cinnamoylhosloppone (52), 3-\textit{O}-benzoylhinokiol (53), and 3-\textit{O}-benzoylhosloquinone (54), Figure 6. The antiplasmodial activities of compound 51 have helped to validate the ethnobotanical use of the plant in the

![Diagram of xanthones and quinones](image)

**Figure 8** Xanthones from African medicinal plants with promising anti-malarial/antiplasmodial activities.
treatment of malaria [78]. The isolation of these compounds was carried out as a result of an ethnomedical use of *H. opposita* in the treatment of malaria. The *n*-hexane extract root bark gave an IC\(_{50}\) of 5.6 μg mL\(^{-1}\) and also exhibited a 26% inhibition of growth of *P. berghei* in mice, at a daily dose of 190 mg kg\(^{-1}\) body weight, for four days [78]. Only compound 51 was tested and showed significant *in vitro* activity against the multidrug-resistant K-1 strain and the chloroquine-sensitive NF54 strain of *P. falciparum*, with IC\(_{50}\) values of 0.4 and 0.22 μg mL\(^{-1}\), respectively. The other metabolites were not screened due to the limited amount available [78].

*Cassia siamea* (Fabaceae) was identified from southwest Nigerian ethnobotany as a remedy for febrile illness. This led to the bioassay-guided fractionation of stem bark of the plant extract, for assessing the *in vitro* anti-malarial activity. Emodin (55) and lupeol were isolated from the ethyl acetate fraction. Both compounds were found to be the active principles responsible for the antiplasmodial property with IC\(_{50}\) values of 5 μg mL\(^{-1}\) respectively [79].

Six quinones were derived from the root bark extract of *Psorospermum glaberrimum* (Hypericaceae) from Cameroon by Lenta et al. [80]. These include glaberianthone (56), 3-geranyloxyemodin anthrone (57), acetylvismione D (58), 2-geranylemodin (59), bianthrone 1a (60), and 3-prenyloxemodin anthrone (61). The *n*-hexane extracts and the isolated compounds were tested *in vitro* for their antiplasmodial activity against *P. falciparum* (W2). The *n*-hexane extract showed good antiplasmodial activity, with IC\(_{50}\) of 0.87 μg mL\(^{-1}\), meanwhile 3-geranyloxymedin anthrone and acetylvismione D showed the best potencies against *P. falciparum* W2 strain with IC\(_{50}\) of 1.68 μM and 0.12 μM, (0.66 μg mL\(^{-1}\) and 0.054 μg mL\(^{-1}\)), respectively. The same authors investigated the root bark of *Harungana madagascariensis* (Hypericaceae), a plant whose roots and bark are used by traditional healers to treat malaria in West Province of Cameroon [81]. These authors isolated bazouanthrone (62), a new anthrone derivative, along with the known compounds, feruginin A (63), harunganol A (64), harunganol A (65), and harunganol B (66). In order to validate its ethnobotanical use, the antiplasmodial activity of the isolated compounds were evaluated in culture against W2 strain of *P. falciparum*. All the compounds were found to be active against the *Plasmodium* parasites with bazouanthrone (62) showing particular potency (IC\(_{50}\) = 1.80 μM).

Makinde et al. investigated the action of extracts of the stem bark of *Spathodea campanulata* (Bignoniaceae) from Nigeria on *Plasmodium berghei berghei* in mice [82]. The blood schizontocidal activity of the extracts was studied in early and established infections using chloroquine as the reference drug. The prophylactic action of the extracts was also investigated with pyrimethamine as the standard drug. The hexane and chloroform extracts of the stem bark showed blood schizontocidal action in both the four-day test and Rane test. The chloroform extract demonstrated some prophylactic properties while the aqueous extract did not show any significant anti-malarial property. In addition, these authors were able to identify the active anti-malarial ingredient to be lapachol (67). The other anti-malarial quinones identified were knipholone (68) and anthrone (69) from *Kniphophia foliosa* (Asphodelaceae) [83,84], as well as 2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-dione (70) and isopinnatal (71) from *Kigelia pinnata*.
Table 4 Summary of promising anti-malarial steroids, lignans, other antiplasmodial compounds derived from African flora

| Compound sub class | Isolated metabolites | Plant species (Family) | Part of plant studied | Place of harvest (City, Country) | Author, Reference |
|--------------------|----------------------|------------------------|-----------------------|---------------------------------|-------------------|
| Steroids           | 91                   | *Ajuga remota* (Lamiaceae) | Aerial parts          | Nairobi, Kenya                   | Kuria et al. [94] |
|                    | 92, 93, 94, 95 and 96| *Vernonia amygdalina* (Asteraceae) | Young pith of trees   | Mahale Mt. National Park, Tanzania | Ohigashi et al. [95] |
| Lignanes           | 97, 98, 99, 100, 101, 102 and 103 | *Pycnanthus angolensis* (Myristicaceae) | Stem bark              | São Tomé and Príncipe islands   | Ramalhete et al. [96] |
|                    | 104                  | *Asparagus africanus* (Asparagaceae) | Roots                 | Kenya                           | Oketch-Rabah et al. [97] |
| Others             | 105                  | *Lippia javanica* (Verbenaceae) | Leaves and stalks     | Limpopo, South Africa           | Ludere et al. [98] |
|                    | 106                  | *Helichrysum cymosum* (Asteraceae) | Whole plant           | South Africa                    | Jakupovic et al. [99] |
|                    | 107, 108, 109 and 110| *Vernonia staehelinoides* (Asteraceae) | Leaves               | Magaliesburg, South Africa      | Pillay et al. [101] |
|                    | 111                  | *Hypericum lanceolatum* (Hypericaceae) | Stem bark             | Mt. Bamboutos, Cameroon          | Zofou et al. [90] |
|                    | 112                  | *Symphonia globulifera* (Clusiaceae) | Seeds                 | Fundong, Cameroon                | Ngouela et al. [92] |
|                    | 113                  | *Morus mesozygia* (Moraceae) | Stem bark             | Centre Province, Cameroon        | Zelefack et al. [61] |
|                    | 114 and 115           | *Kigelia africana* (Bignoniaceae) | Stem bark             | Bandjoun, Cameroon               | Zofou et al. [64,65] |
|                    | 116 and 117           | *Glossocalyx brevipes* (Morimiaeae) | Leaves               | Kumba, Cameroon                  | Mbah et al. [102] |
|                    | 118                  | *Asparagus africanus* (Asparagaceae) | Roots                | Kenya                           | Oketch-Rabah et al. [97] |
|                    | 119                  | *Dracaena manni and Dracaena arborea* (Dracaenaceae) | Seed pulp            | Nigeria                         | Okunji et al. [103] |
(Bignoniaceae) [85]. These compounds were tested against chloroquine-sensitive (T9 − 96) and -resistant (K-1) *P. falciparum* strains and for cytotoxicity using KB cells. Compound 70 possessed good activity against both strains [IC₅₀ values 627 nM (K1), 718 nM (T9 − 96)]. Iso-
pinnatal (71) and the co-occurring kigelinol and isokigelinol exhibited lower activity against both strains. Bringmann et al. also reported that knipholone (68) and three of its natural derivatives from the same plant, as well as seven structurally related but simplified compounds, have been examined for their antimalarial activity against asexual erythrocytic stages of two strains of *P. falciparum* in vitro (K1/chloroquine-resistant and NF 54/chloroquine-sensitive) [84]. All the phenylnaphthoquinones showed considerable activity, with only little cytotoxicity, while their anthraquinone and phenyl moieties were completely inactive.

**Coumarins**

Anti-malarial coumarins have been identified by Cubukcu et al. [86] and by Noster et al. [87] from *Vernonia brachycalyx* (Asteraceae) and *Toddalia asiatica* (Rutaceae), respectively. Cubukcu et al. identified two isomeric 5-methylcoumarins from the roots of *V. brachycalyx*; 20-
$\text{epi}$-cycloisobrachycoumarinone epoxide (72) and cycloiso-
brachycoumarinone epoxide (73), Table 3 and Figure 7. The results of the antimalarial assays against the chloroquine-susceptible D7 and chloroquine- resistant Dd2 strains of *P. falciparum*, showed that compound 72 was weakly active, with IC₅₀ values of 160 μM and 54 μM, while for compound 73, the IC₅₀ values were 111 μM and 54 μM, respectively. Noster et al. also isolated compound 73 from the ether extract of *Exostema caribaeum* but however only moderate activity [87]. In addition, Oketch-Rabah et al. isolated a new anti-malarial coumarin, 5,7-dimethoxy-8-(30-hydroxy-30-methyl-10-butene) coumarin (74), from the roots of *Toddalia asiatica* [87]. This compound showed moderate activity against the chloroquine-sensitive K39 and chloroquine-resistant V1/S strains of *P. falciparum* strains, with IC₅₀ values of 16.2 μg mL⁻¹ and 8.8 μg mL⁻¹, respectively.

The anti-malarial coumarin 7-hydroxy-6-methoxycou-
marin or scopoletin (75) was isolated from the dichloro-
methane leaf extract of *Schefflera umbellifera* (Araliaceae), harvested from Limpopo, South Africa by Mthembu et al. [89]. This compound was evaluated in vitro against both the chloroquine-susceptible (D10) and chloroquine-
resistant (K-1) strains of *P. falciparum* for anti-malarial activity, with an IC₅₀ value of 28.2 μg mL⁻¹.

**Xanthones**

The anti-malarial xanthones; 5-hydroxy-3-
methoxyxanthone (76) and 3-hydroxy-5-methoxyxanthone (77) were isolated from stem bark of *Hypericum lanceolatum* (Hypericaceae) from Cameroon by Zofou et al. [90], with IC₅₀ values of 13.56 μg mL⁻¹ and 8.28 μg mL⁻¹, respectively, on the multidrug-resistant W2mef strain of *P. falciparum*. Six other anti-malarial xanthones were isolated from the methanol extract of the stem bark of *Allanblackia monticola* (Guttiferae) from Cameroon, by Azebaze et al. [91]. These included allanxanthone C (78), garciniafuran (79), tovophyllin A (80), rubraxanthone (81), norcowanin (82) and mangostin (83), Figure 8. Allanxanthone C exhibited an IC₅₀ of 1.3 μM on FcM29 and an IC₅₀ of 6.9 μM on F32. The molecules with interesting activities are known to be norcowanin (IC₅₀ of 6.3 μM on F32) and mangostin (IC₅₀ of 4.1 μM on FcM29 and IC₅₀ of 7.8 μM on F32 [91]. More interestingly, these molecules showed no significant toxicity against the hu-
man melanoma cell A375 cell-line. The antimalarial activities of xanthones isolated from the seed shells of *Symphonia globulifera* were reported against the W2 *Plasmodium* sp. with respective IC₅₀ values of 3.53, 1.29 and 3.17 μM, for gaboaxanthone (84), symphonin (85) and globuliferin (86) [92]. Bioassay-guided fractionation of the fruit pericarp of *Pentadesma butyracea*, using the
antiplasmodial test, led to the isolation of a new bioactive xanthone, named pentadexanthone (87) (IC$_{50}$ = 3 µM against W2), together with three known compounds: cratoxylone (88) (IC$_{50}$ = 2.89 µM), α-mangostin (89) (IC$_{50}$ = 2.77 µM), and garcinone E (90) (IC$_{50}$ = 0.41 µM) [93].

**Steroids**

The steroid, ergosterol-5,8-endoperoxide (91), isolated from the aerial parts of Ajuga remota, exhibited high antiplasmodial activity against the chloroquine-sensitive P. falciparum, with an IC$_{50}$ value of 8.2 µM [94]. Steroidal saponins with anti-malarial activity have also been isolated from the leaves of Vernonia amygdalina [95]. Ohigashi et al. reported the isolation of vernonioside A1 (92), A2 (93), A3 (94), A4 (95) and B1 (96), Figure 9 and Table 4. These saponins had weak antiplasmodial activity against the multidrug-resistant K-1 strain of P. falciparum, with IC$_{50}$ values of 139.7, 94.1, 245.1, 81.8 and 46.1 µg mL$^{-1}$, respectively [95]. These saponins are also reported to be the bitter compounds in the leaves of V. amygdalina.

**Lignans**

*Pycnanthus angolensis* (Myristicaceae) is a plant used in traditional medicine against several diseases. Its bark has been used to treat fever and malaria in São Tomé and Príncipe islands. Ramalhete et al. submitted the dichloromethane extract of the bark to anti-malarial screening and observed an activity against 3D7 P. falciparum strain (IC$_{50}$ = 1.6 µg mL$^{-1}$) [96]. This was further subjected to chromatographic bioguided fractionation, yielding the lignans 4,4′-dihydroxy-3-methoxylignan (97), (−)-dihydroguaiaretic acid (98), 4′-hydroxy-3,3′,4-trimethoxylignan (99), 4,4′-diacetyl-3,3′-dimethoxy lignan (100), talamuidin (101), hinokinin (102), and heliobuthalmin (103), Figure 10, along with the labdane diterpene ocy acid and the steroids stigmast-4-en-β-ol-3-one, stigmasterol and β-sitosterol. Furthermore, other compounds were obtained by derivatization. The *in vitro* anti-malarial activity of the compounds was evaluated against 3D7 and Dd2 P. falciparum strains. The best *in vitro* anti-malarial activity of the compounds was exhibited by compound 97 against the 3D7 strain (IC$_{50}$ = 3.10 µg mL$^{-1}$) and by compound 101 against the Dd2 strain (IC$_{50}$ = 20.7 µg mL$^{-1}$).

*Asparagus africanus* (Asparagaceae) is used by the Akamba tribe in Kenya to treat malaria. A bioassay-guided fractionation of the root extract led to the isolation of the lignan nysol (104), along with the sapogenin muzanzagenin (119). Figure 11, as the bioactive compounds responsible for the anti-malarial activity of this plant [97]. Nysol moderately inhibited *P. falciparum* schizonts with the IC$_{50}$ of 49 µM, while muzanzagenin showed a moderate *in vitro* activity against four different malaria schizont strains the IC$_{50}$ values were 16, 163, 23, and 16 µM, respectively.

**Others**

Lippialactone (105), derived from the ethyl acetate extract of aerial parts of *Lippia javanica*, harvested from South Africa, was shown to be active against the chloroquine-sensitive D10 strain of *P. falciparum* with an IC$_{50}$ value of 9.1 µg mL$^{-1}$, and is also mildly cytotoxic [98]. Helihumulone (106) was derived from extracts of the whole plant of *Helichrysum cynosum* (Asteraceae) from South Africa by Jakupovic et al. [99] and Vuuren et al. [100].

The dichloromethane extract of the leaves of *Vernonia staehe- linoide* (Asteraceae) showed *in vitro* activity (IC$_{50}$ ~ 3 µg mL$^{-1}$) against the chloroquine-sensitive D10 and the chloroquine-resistant (K-1) strains of *P. falciparum* [101]. Pillay et al. further investigated the extract by bioassay-guided fractionation and two structurally related hirsutinolides displaying *in vitro* antiplasmodial activity (IC$_{50}$ ~ 0.2 µg mL$^{-1}$ against D10) were isolated. These were 8α-(2-methylacryloyloxy)-3-oxo-1-desoxy-1,2-dehydrohirsutinolide-13-O-acetate (107), and 8α-(5′-acetoxyenecioxyloxy)-3-oxo-1-desoxy-1,2-dehydrohirsutinolide-13-O-acetate (108). These were found to be cytotoxic to mammalian Chinese hamster ovarian (CHO) cells at similar concentrations, but proved to be attractive scaffolds for structure-activity relationship studies. Two main privileged substructures, a 2(5H)-furanoate unit and a dihydouran-4-one unit, were identified as potential pharmacophores, which may be responsible for the observed biological activity. Mucocloric and mucobromic acids were selected as appropriate 2(5H)-furanoate substructures and these were shown to have comparable activity against the D10 and superior activity against the K1 strains relative to the hirsutinolide natural product. Mucocloric and mucobromic acids (109 and 110) also showed selective cytotoxicity to the malaria parasites compared to mammalian (CHO) cells *in vitro*. The antiplasmodial data obtained with respect to these two acids suggest that the 2(5H)- furanoate substructure is a key pharmacophore in the observed antiplasmodial activity. The identification of antiplasmodial hirsutinolides from *V. staeheleanoides* suggests that they may play a role in the medicinal properties of the plant, but their potential for the development of anti-malarial drugs is limited due to inherent cytotoxicity and lack of selectivity. The results did however lead to the identification of potential pharmacophores, a 2(5H)-furanoate unit and a dihydouran-4-one unit.

The benzophenone 2,5,2′,6′-tetrahydroxybenzenophenone (111), from the stem bark of *Hypericum lanceolatum* (Hypericaceae), exhibited an interesting activity against the multidrug-resistant strain W2meF, with an IC$_{50}$ of 13.56 µg mL$^{-1}$ [90]. Ngouela et al. isolated guttiferone A
from the seeds of *Symphonia globulifera* (Clusiaceae) [92]. This compound exhibited activity against the W2 *Plasmodium* sp. with IC$_{50}$ of 3.17 μM. Mulberrofuran F (113), from the stem bark of *Morus mesozygia* (Moraceae), was active against FcB1-Columbia strain, considered to be resistant against chloroquine, with IC$_{50}$ of 2.6 μgm L$^{-1}$ [65]. Atranorin (114) and specicoside (115), derived from the stem bark extract of *Kigelia africana* (Bignoniaceae) [68,69], were both active against the multidrug-resistant W2mef strain of *P. falciparum* with respective IC$_{50}$ values of 0.67 μgm L$^{-1}$ and 0.52 μgm L$^{-1}$.

The homogentisic acid derivatives methyl 2-(1′β-geranyl-5′β-hydroxy-2′-oxocyclohex-3′-enyl) acetate (116) and 2-(1′β-geranyl-5′β-hydroxy-2′-oxocyclohex-3′-enyl) acetic acid (117) were isolated by Mbah et al. from the leaves of *Glossocalyx brevipes* (Monimiaceae) [102]. Compounds 116 and 117 exhibited both anti-malarial [102] and antisalmonelal activities [104]. The sapogenin muzanzagenin (118) and the saponin spiroconazole A (119), respectively isolated from *Asparagus africanus* (Asparagaceae) [97] and from the West Africa ‘soap tree’ *Dracaena* sp. (Dracaenaceae) [103], also demonstrated significant anti-malarial activities. Spiroconazole A is
reported to exhibit pronounced antileishmanial, anti-malarial and molluscicidal activities.

Conclusions
In this review, an attempt has been made to summarise the main finding of several research groups engaged in the search for naturally occurring active principles from African medicinal plants against *P. falciparum*. With multiple resistance developed by the malaria parasite, the cry has been towards obtaining new effective drugs. Attempts to develop ‘green pharmacies’ for improved phytomedicines against malaria are being encouraged by some NGOs and governments as part of their efforts to control malaria [105]. Additionally, modern hit/lead discovery efforts for specific anti-malarial drug targets are being encouraged. The trend has been towards accelerating this process by employing computer-based methods such as docking, virtual screening, pharmacophore modelling and binding-free energy calculations for hit/lead identification and combinatorial design of novel inhibitors against known anti-malarial drug targets. The practice of virtual screening is beginning to occupy the centre of drug discovery efforts [106] and it has been verified that developing NP libraries containing readily available compounds for screening virtual hits could be highly useful [107]. The authors of this paper have been developing NP databases containing three-dimensional structures of compounds derived from plants used in ATM [108-110] and using computed molecular descriptors to attempt to predict the pharmacokinetic profiles of NPs [110-112]. Since the role of NPs in drug discovery cannot be overemphasized [111-116], efforts are aimed at providing tools for research groups engaged in anti-malarial drug discovery, beginning with NPs derived from African medicinal plants. This is aimed at cutting down the cost of drug discovery when computational and ‘wet lab’ approaches are combined [117,118]. The intention is to make the current collection of three-dimensional structures of naturally occurring anti-malarials from African medicinal plants available for virtual screening. This shall be the scope of part III of this series.

Abbreviations
ADMET: Absorption, distribution, metabolism, excretion and toxicity; ATM: African traditional medicine; DMPK: Drug metabolism and pharmacokinetics; FAS II: Fatty acid synthase II; NP: Natural product; WHO: World Health Organization; WM: Western medicine.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
FNK, LLL, JCN, and LMM conceived the idea. FNK, LLL and PAO participated in data collection. FNK and PAO contributed to data analysis, discussion of results and the conception of the paper under the supervision of LMM, WS, LLL, and JCN. FNK and PAO wrote the first draft of the paper and all authors agreed on the final version before submission.

Acknowledgements
Financial support is acknowledged from Lhasa Ltd, Leeds, UK through the Chemical and Bioactivity Information Centre (CBIC), University of Buea, Cameroon.

Author details
1 Chemical and Bioactivity Information Centre, Department of Chemistry,Faculty of Science, University of Buea, PO Box 63, Buea, Cameroon.
2 Department of Pharmaceutical Sciences, Martin-Luther University of Halle-Wittenberg, Wolfgang-Langenbeck Str. 4, 06120 Halle, Saale, Germany.
3 Department of Chemistry, Faculty of Science, University of Douala, PO Box 24157, Douala, Cameroon.

Received: 31 October 2013 Accepted: 25 February 2014
Published: 6 March 2014

References
1. Nogueira CR, Lopes LMX: Antiplasmodial natural products. Molecules 2011, 16:2146–2190.
2. White NJ: Antimalarial drug resistance. J Clin Invest 2004, 113:1084–1092.
3. WHO: World Malaria Report 2012. Geneva: World Health Organization; 2012.
4. Vogel G: Infectious disease - new map illustrates risk from the ‘other’ malaria. Science 2010, 329:618–618.
5. Addae-Mensah I, Fakorede F, Hottie A, Nwaka S: Traditional medicines as a mechanism for driving research innovation in Africa. Malar J 2011, 10(Suppl 1):59.
6. Guantai E, Chibale K: How can natural products serve as a viable source of lead compounds for the development of new/ novel anti-malarials? Malar J 2011, 10(Suppl 1):52.
7. Cruz LR, Spangenberg T, Lacerda MVG, Wells TNC: Malaria in South America: a drug discovery perspective. Malar J 2013, 12:168.
8. Chin YW, Balunas MJ, Chai HB, Kinghorn AD: The value of plants used in traditional medicine for drug discovery. Environ Health Perspect 2001, 109(suppl 6):73–79.
9. Ginsburg H, Deharo E: A call for using natural compounds in the development of new antimalarial treatments-an introduction. Malar J 2011, 10(Suppl 1):51.
10. Wells TNC: Natural products as starting points for future anti-malarial therapies: going back to our roots? Malar J 2011, 10(Suppl 1):53.
11. Anthony MP, Burrows JN, Duparc S, Joehrele J, Wells TNC: The global pipeline of new medicines for the control and elimination of malaria. Malar J 2012, 11:316.
12. Hostettmann K, Marston A, Ndjoko K, Wolferder JL: The potential of African plants as a source of drugs. Curr Org Chem 2000, 4:973–1010.
13. Efange SMN: Natural products: a continuing source of inspiration for the medicinal chemist. In Advances in Phytomedicine. Edited by Iwu MM, Wootton JC. Amsterdam: Elsevier Science; 2002:61–69.
14. Tona L, Ngimbi NP, Tsakala M, Mesia K, Cimanga K, Apers S, De Bryune T, Pieters L, Totte J, Vlietinck AJ: Antimalarial activity of 20 crude extracts from nine African medicinal plants used in Kinshasa, Congo. J Ethnopharmacol 1999, 68:193–203.
15. Tonial L, Cimanga RK, Mesia K, Musamba CT, De Bryune Apm TS, Henmans N, Van Miert S, Pieters L, Totte J, Vlietinck AJ: Antimalarial activity of 20 crude extracts from seven medicinal plants used in the Democratic Republic of Congo. J Ethnopharmacol 2004, 93:27–32.
16. Dike IP, Oyenbe OE, Adeyibi FE: Ethnobotanical survey for potential anti-malarial plants in south-western Nigeria. J Ethnopharmacol 2012, 144:618–626.
17. Iwu MM, Figueredo P, Do Rosário VE, Amaral AC, Lopes D: A review of antimalarial plants used in traditional medicine in communities in Portuguese-Speaking
countries: Brazil, Mozambique, Cape Verde, Guinea-Bissau, São Tomé and Príncipe and Angola. Mem Inst Oswaldo Cruz 2011, 106(Supp1):142–158.

21. Ancillo C, Azas N, Mahiou V, Olliver E, Di Giorgio C, Keita A, Timon-David P, Balansard G: Antimalarial activity of extracts and alkaloids isolated from six plants used in traditional medicine in Mali and Sao Tome. Phytother Res 2002, 16:456–649.

22. Puri M, Masum H, Heys, J, Singer PA: Harnessing biodiversity: the Malagasy Institute of Applied Research (IMRA). BMC Int Health Hum Rights 2010, 10(Suppl 1):59.

23. Rasoanarivo P, Ratsimamanga-Urverg S, Ramaratirahimisaibol D, Rafatro H, Rakoto-Ratimamanga A: Criblage d’extraits de plantes de Madagascar pour recherche d’activité antipaludique et d’effet potentielisateur de la chloroquine. J Ethnopharmacol 1999, 64:117–126.

24. Mbatchi SF, Mbatchi B, Banzouzi JT, Banonma T, Noorde Ntandou GF, Ouamba JM, Berly A, Benoit-Valc F: In vitro antiparasitological activity of 18 plants used in Congo Brazzaville traditional medicine. J Ethnopharmacol 2004, 106:168–174.

25. Randriananarivo M, Raisidimana VT, Rabarison H, Chepogoi PK, Ratsimbason M, Mulhoodan DA, Mclulare P: Plants traditionally prescribed to treat tazö (malaria) in the eastern region of Madagascar. Malar J 2003, 2:25.

26. Kumulungui BS, Ondo-Azi AS, Mintsa NA, Fumoza F, Traore A: In vitro antiparasitological activity of seven plants commonly used against malaria in Burkina Faso. J Med Plant Res 2012, 6:2288–2284.

27. Bero J, Ganfon H, Jonville MC, Frédérich M, Gbaguidi F, DeMol P, Mbatchi SF, Mbatchi B, Banzouzi JT, Bansimba T, Nsonde Ntandou GF, Kuete V, Efferth T: Antimalarial agents from plant extracts traditionally used in Benin in traditional medicine to treat malaria. J Ethnopharmacol 2009, 122:439–444.

28. Pillay P, Maharaj VI, Smith PJ: Investigation South African plants as a source of antimalarial drugs. J Ethnopharmacol 2008, 129:438–454.

29. Soh PN, Benoît-Vical F: Are West African plants a source of future antimalarial drugs? J Ethnopharmacol 2007, 114:130–140.

30. Muthura CN, Rukunga GM, Chhabra SC, Mungai GM, Njagi ENM: Traditional antimalarial phytopharmacy remedies used by the Kayale community of the Kenyan Coast. J Ethnopharmacol 2007, 114:377–386.

31. Vonron-Sénéchou C, Weniger B, Ouattara M, Bi FT, Kamenan A, Lobstein A, Brun R, Anton R: In vitro antiparasitological activity and cytotoxicity of ethnobotanically selected Ivorian J. J Ethnopharmacol 2003, 87:221–225.

32. Waako PJ, Katutura E, Smith P, Folk P: East African medicinal plants as a source of lead compounds for the development of new antimalarial drugs. Afr J Ecol 2007, 45(Suppl 1):102–106.

33. Maregesi S, Van Miert S, Pannecouque C, Haddad MHF, Hermans N, Wright C, Vletinck AJ, Apers S, Pieters L: Screening of Tanzanian medicinal plants against Plasmodium falciparum and human immunodeficiency virus. Mem Inst Oswaldo Cruz 2009, 104:689–694.

34. Weenen H, Nkunya MH, Bray DH, Mwasumibi LB, Kinabo LS, Kilimili VAEB: Antimalarial activity of Tanzanian medicinal plants. Planta Med 1990, 56:365–370.

35. Kuete V, Effront T: Cameroonian medicinal plants: pharmacology and derived natural products. Front Pharmacol 2010, 1:123.

36. Ntie-Kang BS, Ondo-Azi AS, Mintsa NA, Mbaizou E, Di Giorgio C, Keita A, Timon-David P, Balansard G: Antimalarial activity of extracts and alkaloids isolated from six plants used in traditional medicine in Mali and Sao Tome. Phytother Res 2002, 16:456–649.

37. Rasoanarivo P, Ratsimamanga-Urverg S, Ramaratirahimisaibol D, Rafatro H, Rakoto-Ratimamanga A: Criblage d’extraits de plantes de Madagascar pour recherche d’activité antipaludique et d’effet potentielisateur de la chloroquine. J Ethnopharmacol 1999, 64:117–126.

38. Mbatchi SF, Mbatchi B, Banzouzi JT, Banonma T, Noorde Ntandou GF, Ouamba JM, Berly A, Benoit-Valc F: In vitro antiparasitological activity of 18 plants used in Congo Brazzaville traditional medicine. J Ethnopharmacol 2004, 106:168–174.

39. Randriananarivo M, Raisidimana VT, Rabarison H, Chepogoi PK, Ratsimbason M, Mulhoodan DA, Mclulare P: Plants traditionally prescribed to treat tazö (malaria) in the eastern region of Madagascar. Malar J 2003, 2:25.

40. Kumulungui BS, Ondo-Azi AS, Mintsa NA, Fumoza F, Traore A: In vitro antiparasitological activity of seven plants commonly used against malaria in Burkina Faso. J Med Plant Res 2012, 6:2288–2284.

41. Bero J, Ganfon H, Jonville MC, Frédérich M, Gbaguidi F, DeMol P, Mbatchi SF, Mbatchi B, Banzouzi JT, Bansimba T, Nsonde Ntandou GF, Kuete V, Efferth T: Antimalarial agents from plant extracts traditionally used in Benin in traditional medicine to treat malaria. J Ethnopharmacol 2009, 122:439–444.

42. Pillay P, Maharaj VI, Smith PJ: Investigation South African plants as a source of antimalarial drugs. J Ethnopharmacol 2008, 129:438–454.

43. Soh PN, Benoît-Vical F: Are West African plants a source of future antimalarial drugs? J Ethnopharmacol 2007, 114:130–140.

44. Muthura CN, Rukunga GM, Chhabra SC, Mungai GM, Njagi ENM: Traditional antimalarial phytopharmacy remedies used by the Kayale community of the Kenyan Coast. J Ethnopharmacol 2007, 114:377–386.

45. Vonron-Sénéchou C, Weniger B, Ouattara M, Bi FT, Kamenan A, Lobstein A, Brun R, Anton R: In vitro antiparasitological activity and cytotoxicity of ethnobotanically selected Ivorian J. J Ethnopharmacol 2003, 87:221–225.

46. Waako PJ, Katutura E, Smith P, Folk P: East African medicinal plants as a source of lead compounds for the development of new antimalarial drugs. Afr J Ecol 2007, 45(Suppl 1):102–106.

47. Maregesi S, Van Miert S, Pannecouque C, Haddad MHF, Hermans N, Wright C, Vletinck AJ, Apers S, Pieters L: Screening of Tanzanian medicinal plants against Plasmodium falciparum and human immunodeficiency virus. Mem Inst Oswaldo Cruz 2009, 104:689–694.

48. Weenen H, Nkunya MH, Bray DH, Mwasumibi LB, Kinabo LS, Kilimili VAEB: Antimalarial activity of Tanzanian medicinal plants. Planta Med 1990, 56:365–370.

49. Kuete V, Effront T: Cameroonian medicinal plants: pharmacology and derived natural products. Front Pharmacol 2010, 1:123.

50. Ntie-Kang BS, Ondo-Azi AS, Mintsa NA, Mbaizou E, Di Giorgio C, Keita A, Timon-David P, Balansard G: Antimalarial activity of extracts and alkaloids isolated from six plants used in traditional medicine in Mali and Sao Tome. Phytother Res 2002, 16:456–649.

51. Puri M, Masum H, Heys, J, Singer PA: Harnessing biodiversity: the Malagasy Institute of Applied Research (IMRA). BMC Int Health Hum Rights 2010, 10(Suppl 1):59.

52. Rasoanarivo P, Ratsimamanga-Urverg S, Ramaratirahimisaibol D, Rafatro H, Rakoto-Ratimamanga A: Criblage d’extraits de plantes de Madagascar pour recherche d’activité antipaludique et d’effet potentielisateur de la chloroquine. J Ethnopharmacol 1999, 64:117–126.
65. Zefelefak F, Gulet D, Valentin A, Fongang RCS, Kom B, Chevalley S, Ngouela SA, Tsamo E, Fabre N, Dijoux-Franca MG. Antiplasmodial and cytotoxic activities of flavonoids and arylbenzofuran derivatives from Morus mesozygia. Greener J Biol Sci 2012, 2:202–04.

66. Banquei JK, Bhayala R, Lenta BN, Youngoue DT, Ngouela SA, Mustafa SA, Asea K, Choudhary MF, Prige ST, Henson R, McNeilly AF, Tsamo E, AY. Plerofuran dimeric and other bioactive constituents from the fígs of Ficus mucuso. J Nat Prod 2011, 74:1320–39.

67. Andayi AW, Yenesew A, Derese S, Midiwo JO, Gitu PM, Jondiko OJI, Akala H, Nsangi B, Duda J, Akula H, Amin D, Ye H, Nihoul C, Karma M, Okoro D, Dijoux-Franca MG. A phytochemical study of Schefflera umbelllfera and Exostema canebreума extracts on Plasmodium falciparum. Planta Med 1999, 65:63–65.

68. Ochek-Rahab HA, Mwango JW, Liganten J, Mbuji EK. A new antimalarial coumarin from Toddalia asiatica roots. Fitzoea 2000, 71:363–640.

69. Mthembu XS. A phytochemical study of Schefíella umbellifera and Elephantouchia elephantína. MSc thesis. Pietermaritzburg, South Africa: School of Chemistry, University of KwaZulu-Natal; 2007.

70. Zofou D, Kowa TK, Wabo HK, Ngemenya MN, Tane P, Titanji VPK. Hypericum lanceolatum (Hypericaceae) as a potential source of new anti-malarial agents: a bioassay-guided fractionation of the stem bark. Malar J 2011, 18:167.

71. Azebaze AGB, Meyer M, Valentin A, Nguemfo EL, Fornum ZT, Neengfack AE. Preliminary xanthone derivatives with antimalarial activity from Allandíacca monticola STÁNER L. C. Pharm Bull 2006, 54:111–113.

72. Ngouela S, Lenta BN, Ngouela S, Tantangmo F, Devkota KP, Boyom FF, Gut J, Rosenthal PJ, Connolly JD. Anti-plasmodial and antioxidant activities of the seed shells of Symphonia globulifera Linn f. Phytochemistry 2006, 67:302–306.

73. Lenta BN, Kamdem LM, Ngouela S, Tantangmo F, Devkota KP, Boyom FF, Rosenthal PJ, Tsamo E. Antimalarial constituents from the fruit pericarp of Pentadesma butyracea. Planta Med 2011, 77:377–379.

74. IPCC KEK, Chepkwony H, Govaerts C, Roets E, Busson R, de Witte P, Zupko I, Hoornaert G, Quiryren L, Maes L, Janssens L, Hoogmartens J, Laekeman G. The antimalarial activity of isolates from Ajuga remota. J Nat Prod 2002, 65:789–793.

75. Chihaghi H, Hoffman MA, Iztuzu D, Koshimizu K, Kawanaka M, Sugiyama H, Kyri G, Warhurst DC, Allen D, Wright CW, Phillipson JD, Timon-David P, Delmas F, Elias R, Balancard G. Toward the chemical ecology of medicinal plant use in chimpanzees: the case of Vernonia amygdalina, a plant used by wild chimpanzees possibly for parasite-related diseases. J Chem Ecol 1994, 20:541–553.

76. Ramalhete C, Abrantes M, Mil-Homens T, Duarte N, Lopes D, Cravo P, Rissotto T, Gouveia J, Boavida L, Gouveia J, Oliveira A, Almeida M, Almeida M. Selective inhibitors of Falcipain 2 and antimalarial activity of Cassia siamea. Fitoterapia 2013, 84:1–7.

77. Senn M, Gunzenhauser S, Brun R, Sequin U. Antiplasmodial compounds from Cassia siamea (Rutaceae). J Nat Prod 2001, 64:543–546.

78. Cheplogoi PK, Mulholland DA, Coombes PH, Randrianarivelojosia M, Kirby GD, Warhurst DC, Allen D, Wright CW, Phillipson JD, Timon-David P, Delmas F, Elías R, Balancard G. Toward the chemical ecology of medicinal plant use in chimpanzees: the case of Vernonia amygdalina, a plant used by wild chimpanzees possibly for parasite-related diseases. J Chem Ecol 1994, 20:541–553.

79. Lanquart A, Stelzner S, Wachsmuth K, Allen D, Wright CW, Phillipson JD, Timon-David P, Delmas F, Elías R, Balancard G. Toward the chemical ecology of medicinal plant use in chimpanzees: the case of Vernonia amygdalina, a plant used by wild chimpanzees possibly for parasite-related diseases. J Chem Ecol 1994, 20:541–553.

80. Lannang AM, Louh GN, Lontsi D, Specht S, Sarite SR, Flörke U, Hussain H, Horsfall A, Krohn K. Antimalarial compounds from the root bark of Garcinia polyantha Oliv. J Antibiot 2008, 61:518–523.

81. Deck LM, Royer RE, Chamblee BB, Hernandez VM, Malone RR, Torres JE, Hunsaker LA, Piper RC, Makler KT, Vander Jagt DL. Selective inhibitors of human lactate dehydrogenases and lactate dehydrogenase from the malarial parasite Plasmodium falciparum. J Med Chem 1991, 34:879–887.

82. Lenta BN, Ngouela S, Boyom FF, Tantangmo F, Tchouya GRF, Tsamo E, Gut J, Rosenthal PJ, Connolly JD. Anti-plasmodial activity of some constituents of Paroaspermum glaberrimum. Chem Pharm Bull 2008, 56:222–226.

83. Makinde JM, Amusan OOG, Adesogun EK. The antimalarial activity of Spatheoa cavanulata stem bark extract on Plasmodium berghei in mice. Planta Med 1988, 54:122–125.

84. Dagne E, Steglich W, Kopenhagen: a unique anthraquinone derivative from Knojiophila falax. Phytochemistry 1984, 23:1720–1723.

85. Bringmann G, Menche D, Bejaalb M, Abeerag BM, Kaminsky R: Antiplasmodial activity of knophiline and related natural phenylanthraquinones. Planta Med 1999, 65:757–758.

86. Weiss CR, Moideen SVK, Croft SL, Houghton PJ. Activity of extracts and isolated naphthoquinones from Kigelia pinnata against Plasmodium falciparum. J Nat Prod 2000, 63:1306–1309.

87. Cubukcu B, Bray DH, Warhurst DC, Meritic AH, Ozhatay N, Sanuy G. In vitro antimalarial activity of crude extracts and compounds from Artemisia abrotanum L. Phytother Res 1990, 4:203–204.

88. Nester S, Kraus L. In vitro antimalarial activity of Coutarea latiflora and Exostema cuneatum extracts on Plasmodium falciparum. Planta Med 1990, 56:63–65.

89. Mthembu XS. A phytochemical study of Schefíella umbellifera and Elephantouchia elephantína. MSc thesis. Pietermaritzburg, South Africa: School of Chemistry, University of KwaZulu-Natal; 2007.

90. Zofou D, Kowa TK, Wabo HK, Ngemenya MN, Tane P, Titanji VPK. Hypericum lanceolatum (Hypericaceae) as a potential source of new anti-malarial agents: a bioassay-guided fractionation of the stem bark. Malar J 2011, 18:167.

91. Azebaze AGB, Meyer M, Valentin A, Nguemfo EL, Fornum ZT, Neengfack AE. Preliminary xanthone derivatives with antimalarial activity from Allandíacca monticola STÁNER L. C. Pharm Bull 2006, 54:111–113.
108. Ntie-Kang F, Mbah JA, Mbaze LM, Lifongo LL, Scharfe M, Ngo Hanna J, Cho-Ngwa F, Onguéné PA, Owono LCO, Megnassan E, Sippl W, Efange SMN: CamMedNP: building the Cameroonian 3D structural natural products database for virtual screening. *BMC Complement Altern Med* 2013, 13:88.

109. Ntie-Kang F, Onguéné PA, Scharfe M, Owono LCO, Megnassan E, Mbaze LM, Sippl W, Efange SMN: ConMedNP: a natural product library from Central African medicinal plants for drug discovery. *RSC Adv* 2014, 4:409–419.

110. Ntie-Kang F, Zofou D, Babiaka SB, Meudom R, Scharfe M, Lifongo LL, Mbah JA, Mbaze LM, Sippl W, Efange SMN: AfroDb: a select highly potent and diverse natural product library from African medicinal plants. *PLoS ONE* 2013, 8e78085.

111. Ntie-Kang F, Mbah JA, Lifongo LL, Owono LCO, Megnassan E, Mbaze LM, Judson PN, Sippl W, Efange SMN: Assessing the pharmacokinetic profile of the CamMedNP natural products database: an *in silico* approach. *Org Med Chem Lett* 2013, 3:10.

112. Ntie-Kang F, Lifongo LL, Mbah JA, Owono LCO, Megnassan E, Mbaze LM, Judson PN, Sippl W, Efange SMN: *In silico* drug metabolism and pharmacokinetic profiles of natural products from medicinal plants in the Congo basin. *In Silico Pharmacol* 2013, 1:12.

113. Koehn FE, Carter GT: The evolving role of natural products in drug discovery. *Nat Rev Drug Discov* 2005, 4:206–220.

114. Harvey AL: Natural products in drug discovery. *Drug Discov Today* 2008, 13:894–901.

115. Newman DJ: Natural products as leads to potential drugs: an old process or the new hope for drug discovery? *J Med Chem* 2008, 51:2589–2599.

116. Li JWH, Vederas JC: Drug discovery and natural products: end of an era or an endless frontier? *Science* 2009, 325:161–165.

117. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Delivery Rev* 1997, 23:3–25.

118. DiMasi JA, Hansen RW, Grabowisk HG: The price of innovation: new estimates of drug development costs. *J Health Econ* 2003, 22:151–185.

doi:10.1186/1475-2875-13-81

Cite this article as: Ntie-Kang et al.: The potential of anti-malarial compounds derived from African medicinal plants, part II: a pharmacological evaluation of non-alkaloids and non-terpenoids. *Malaria Journal* 2014 13:81.