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Antiplasmodial compounds from Millettia dura

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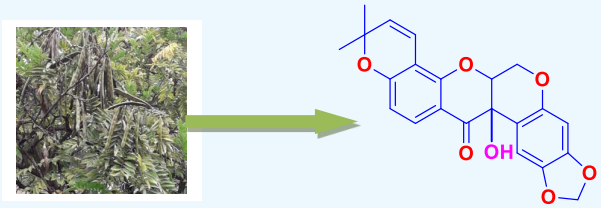
ABSTRACT

Malaria still poses a big challenge to the health care of many tropical countries. The plasmodium resistance to the conventional drugs is the major hitch in its treatment. Higher plants have produced single line antimalarials and given important lead molecules. On this basis, flavonoids isolated from millettia dura by chromatographic techniques were screened against W2 and D6 strains of plasmoduim falcipalum. Both, the crude and pure compounds tested showed mild activities against the test organisms. The crude extract of the stem bark had the highest respective activity of 63.7±8.6 and 46.1±4.5 µg/ml against W2 and D6. Of the pure compounds, milletosin was active towards both W2 and D6 with a respective IC50s of 87.9±8.9 and 66.70±30.3 µg/ml. Synergistic effect might have contributed to the relative high activity of the crude than the pure compounds. Basing on the structure activity relationship of the tested compounds, suitable structural modification could be ideal to enhance the antiplasmodial activity.

Graphical Abstract



Keywords: *Malaria, antiplasmodial, millettia dura, higher-plants and antimalarial-resistance.*

Introduction

Malaria is the most lethal of the tropical diseases caused by protozoan parasites (Moukénet *et al.*, 2022; Omole *et al.*, 2018), the others being toxoplasmosis, amoebiasis, leishmaniosis, and trypanosomiasis (Mushtaque & Shahjahan, 2015; Nogueira & Lopes, 2011).

The world malaria report of 2020, records a 60% fall in the global malaria mortality between 2000 and 2019. In this period, African Region realized an extraordinary decline in her annual death toll from malaria from 680 000 to 386 000 (WHO 2020). However, due to disruption in, WHO projected that there could be 46,000 additional deaths as a result of a 25% disruption in treatment or any other single intervention due to COVID-19 (WHO 2020).

According to Dr Tedros Adhanom Ghebreyesus the Director-General of World Health Organization, "There were an estimated 14 million more malaria cases and 47,000 more deaths in 2020 compared to 2019", which he attributed to service disruptions during the pandemic (WHO 2021). Indeed, it has been reported that there were an estimated 241 million malaria cases (WHO 2022) resulting into 627 000 deaths globally in 2020 alone (Sangbakembi-Ngounou *et al.*, 2022). Africa (Otambo *et al.*, 2022) including Uganda (Achan *et al.*, 2022), contributed 95% of the global malaria burden in 2020. As of now, every 3 out of the 10 visits to a health facility in Uganda is due to malaria. This shift of events calls for a different intervention, possibly a home grown solution from the rich African flora (Buyinza & Gumula, 2022). The world partners now demand governments most affected by malaria to own up the challenge, this brings malaria to the list of the neglected tropical diseases.

The immunal compromised population of the world is the most vulnarable (WHO 2018). A case in point is the over 260,000 under five African children who die due to malaria annually (WHO 2021). The poor in less developed countries (Bhutta *et al.*, 2014; Makoge *et al.*, 2017) are the most affected of which Africa contributes over 93% (Otambo *et al.*, 2022) of the total global malaria burdden. Plasmodium *falciparum* is the most devastating parasites in Africa (99.7% deaths in 2017) and Plasmodium *vivax* causes 71.4% of all the malaria cases in America (WHO 2018; Omole *et al.*, 2019 & 2018; Nogueira and Lopes 2011).

As of old, quinine has been used effectively on both evils and later chloroquine. However, the parasites developed resistance to these drugs and the alternative drugs developed could not match the pharmacological profile of the old drugs. This invited more alternative treatments and combination therapies (CT). Artemisinin as the new alternative antimalarial has also registered resistance in many countries in Africa including East Africa (Arya *et al.*, 2021; Rosenthal, 2018; Tumwebaze *et al.*, 2021). Resistance to the recommended artemisinin combination therapy (ACTs) has also been reported in Southeast Asia and some parts in Africa (Arya *et al.*, 2021; Omole *et al.*, 2019) including Northern Uganda (Ikeda *et al.*, 2016) and yet some CTs pose cardiotoxicity challenges (Mushtaque, 2015; Vandekerckhove & Matthias, 2015).

Anti-malarial drug resistance has become a major hitch in malaria control over the WHO endemic zones leading to the spread of malaria to new zones and re-emergence in areas where it had previously been controlled (PAHO/WHO, 2018; Omole *et al.*, 2019). Vectors are also becoming more adaptive by changing their biting pattern to when people are most unprotected, in the evenings, early mornings and outdoors (Sangbakembi-Ngounou *et al.*, 2022).

Many other interventions have been sought including vaccination, in which over 2.4 million doses of malaria vaccine trials have been rolled out in the endemic areas of three African countries. Satisfactory reports on safety and effectiveness has been reported but this has not seen massive vaccination campaigns rolled out (World malaria report 2021). In the same way, intentional search of antimalarial lead molecules has been intensified. Between 2010 and 2017, a total of 1524 compounds from 397 plants were assayed against one or more *Plasmodium* strain. Interestingly, 29% of the test compounds showed an IC50 ≤ 3.0 μM towards different *Plasmodium* strain. This informs the potential of several of these compounds to be developed into feasible antimalarial drugs (Tajuddeen & Van Heerden, 2019).

The fact that massive vaccination against malaria has not been rolled out and that plants offer lead molecules of high potency, there is then need to intensify the search for new and cheaper antimalarial drugs from nature with different modes of action to mitigate the drug resistance.

Literature Review

Antimalarial from Nature

Antimalarial from nature or their derivatives have been at the forefront in the fight against malaria. The most prominent of these include quinine (1), chloroquine (2), artemisinin (3), primaquine (4), mefloquine (5), Figure 1 and their combinations (Baird, 2005; Woodrow, 2005; Kumar *et al.*, 2014, Vandekerckhove & hooghe, 2015, Bruce *et al.*, 1950). The aminoquinoline antimalarial drug quinine (1) was isolated from *Cinchona succiruba* (Rubiaceae) in 1812 and it became the cornerstone for development of modern antimalarial. An era of organic synthesis followed leading to the development of aminoquinoline-based synthetic antimalarial such as chloroquine (2), primaquine (4), mefloquine (5), amodiaquine (6) and quinidine (7) using quinine (1) as a template (Willcox *et al.*, 2004). In 1946, a quinazolin alkaloid, febrifugine (8) said to be 100-times more active than quinine was isolated from *Dichroa febrifuga* (Willcox *et al.*, 2004). However, up to now its development into antimalarial has been limited by its side effects (Willcox *et al.*, 2004). In 1971, another important antimalarial, a sesquiterpene lactone, artemisinin (3) was isolated from *Artemisia annua* (Woodrow, 2005). More effective artemisinin based semisynthetic antimalarial such as artemether (9), arteether (10), sodium artesunate (11) and Cinconine (12) have been developed (Willcox *et al.*, 2004). The search for antimalarial from nature is still an active research.

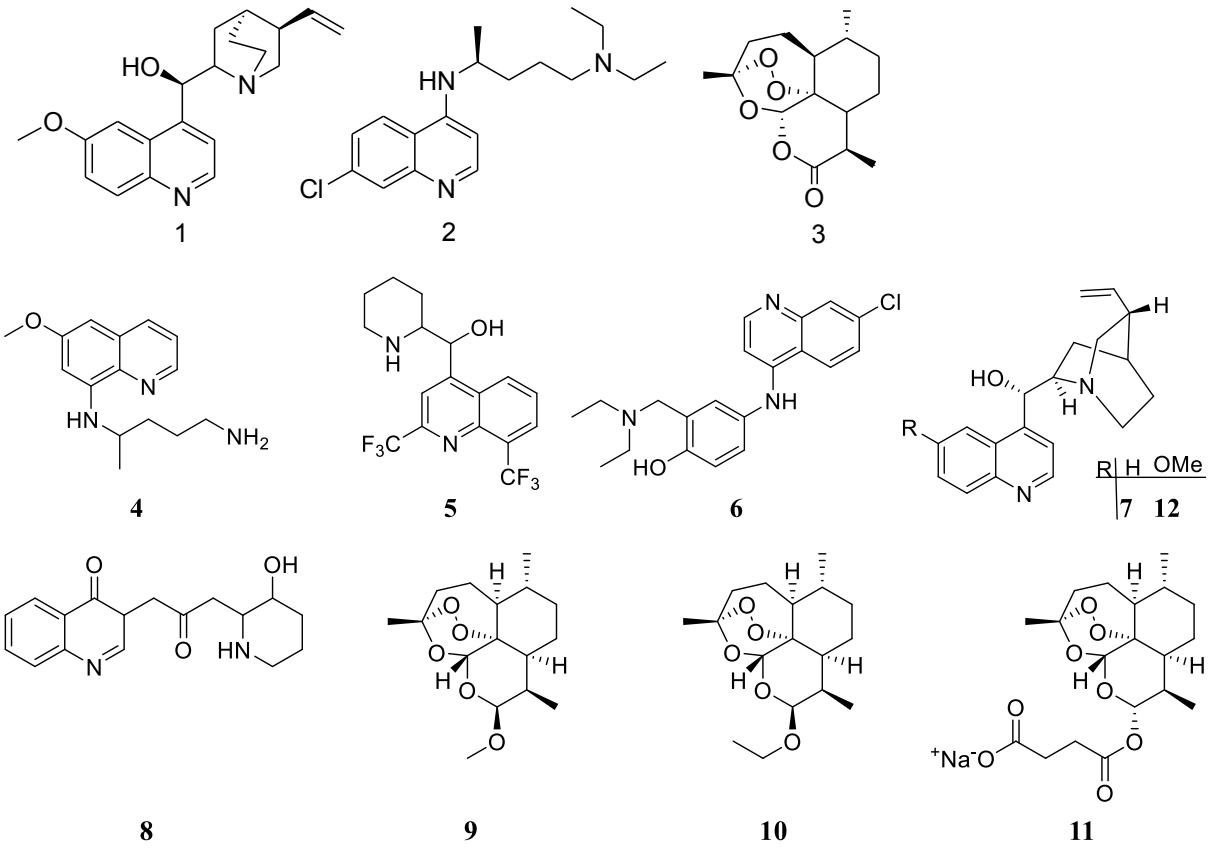


Figure 1: Antimalarials from higher plants and their derivatives

Resistance to Antimalarial

The success in the management and or elimination of malaria was hindered by the early emergence of drug resistant *Plasmodium* strains. *Plasmodium* resistance to drugs has been growing at a rate much higher than the development of new antimalarial. Antimalarial drug resistance has been reported for *P. falciparum*, *P. vivax*, and *P. malariae* (Gunjan *et al.*, 2017; White *et al.*, 2014). In Table 1 a brief overview of the time of the likely onsets of resistance to some conventional antimalarial is given.

Table 1: Time of resistance onsets to some antimalarial (data from Gunjan *et al.*, 2017)

Antimalarial	Time introduced	First report of resistance	Place of first occurrence
Quinine	1820	1925	S. America
Chloroquine	1947	1957	Thai-Cambodia boarder
Fansidar	1979	1980	
Mefloquine	1974	1987	
Artemisin	1972	2008	

Owing to mutation and travel patterns, the problem of Plasmodium resistance to first line antimalarial and their combination therapies has since then spread to other malaria endemic regions including Africa (Cooper *et al.*, 2018). A search therefore for new antimalarial with a different mode of action is an immediate necessity.

Materials and Methods

Plant Material

The flowers, seedpods, stem and root bark of *M. dura* (Figure 2) were collected from Chiromo campus, the University of Nairobi. The plant was identified by Mr. Patrick Mutiso Kyalo, School of Biological Sciences University of Nairobi.

Figure 2: Picture of Millettia dura (taken by Buyinza in 2018)

Extraction and Purification of Compounds from the Flowers of *M. dura*

The air dried and pulverized flowers of M. dura (1.8 kg) were extracted (4 x 24hrs) by cold percolation using six liters of dichloromethane/methanol (1:1 v/v). A crude extract 209.38g (11.6% yield) was obtained after concentration. 150g of the crude was fractionated by column chromatography over 600g of silica gel hexane slurry and eluting with increasing percentages of ethyl acetate in hexane.

Nine known compounds were isolated and characterized (Buyinza 2020 a).

Extraction and purification of compounds from the seed pods of *M. dura*

The air dried and ground seed pods of M. dura (2.5 kg) were exhaustively extracted by cold percolation using eight liters of dichloromethane/methanol (1:1 v/v). This gave 238.13g (9.5% yield) of a dark brown crude extract after concentration on a rotary evaporator. A portion of 200g of the crude extract was fractionated by column chromatography using n-hexane in increasing percentages of ethyl acetate. Seven compounds (three rotenoids and four isoflavones) were isolated from the seed/pods of M. dura as described in (Buyinza 2020 a).

Extraction and purification of compounds from the stem bark of *M. dura*

Four kilograms (4kg) of the air dried and pulverized stem bark of M. dura were extracted by cold percolation (6x24hrs) using 12 liters of dichloromethane/methanol (1:1 v/v). This gave 410.98g (10.3% yield) of a brown crude extract after concentration. A portion of 300g of the crude extract was fractionated by column chromatography using hexane in increasing percentages of ethyl acetate. Fourteen compounds were isolated and characterized from the stem bark of M. dura as described in (Buyinza 2020 a).

In vitro Antiplasmodial Activity

A semi-automated micro-dilution assay technique that measures the ability of the compounds to inhibit incorporation of [G-3H] hypoxanthine into the malaria parasite was used (M. O'Neill *et al.*, 1985; M. J. O'Neill *et al.*, 1986). The parasites were cultured by a method earlier described by (Trager & Jensen, 1976). Both D6 (chloroquine sensitive) and W2 (chloroquine resistant) plasmodium strains were used. Parasites were cultured in sealed flasks at 37°C, in a 3% O_2, 5% CO_2 and 92% N_2 atmosphere in RPMI 1640, 25 mM HEPES, pH 7.4, supplemented with heat inactivated 10% human serum and human erythrocytes to achieve a 3% haematocrit. On attainment of ring stage, parasites were synchronized with 5% sorbitol and tested at 0.4% parasitemia passage into 96-well plates. Stock solutions of compounds were prepared at 1mg/ml in DMSO diluted by RPM1640 to attain 0.2% DMSO and tested in triplicate as done by (Desjardins, 1979). Equal concentration of DMSO was used as negative control while 1.1µm artemisinin served as positive control. The cultures were then incubated for 48 hours at 37°C. Thereafter, each well was pulsed with 25 µL of culture medium containing 0.5 µCi of [G-3H]-hypoxanthine and the plates incubated for a further 18 hours. The contents of each plate were harvested onto glass fibre filters, washed thoroughly with distilled water, dried and radioactivity measured using a scintillation counter.

Results and discussion

Phytochemical investigation of the flowers of *Millettia dura* resulted in the identification of six known isoflavones; calopogonium isoflavone A, jamaicin, durmillone, durallone, ichthynone, formononetin and 6-methoxycalopogoniumisoflavone A (Buyinza *et al.*, 2019). The flavonol kampferol and the chalcone 4,2′-dihydroxy-4′-methoxychalcone were also obtained (Buyinza *et al.*, 2020 b).

From the seedpods of *mellettia dura*, seven compouds were isolated. Four isoflavones calopogonium isoflavone A, jamaicin, durallone and 6-methoxycalopogoniumisoflavone A plus three rotenoids, Milletone, Milletosin and Tephrosin (Buyinza, 2020 a).

Fourteen compounds were isolated and characterized from the stem bark of millettia dura. Isoerythrin-A-4′-(3-methylbut-2-enyl) ether, Maximaisoflavone J, Ferrugone, Psuedoferrugone, Barbigerone, Maximaisoflavone D, Maximaisoflavone G and (±) Deguelin were isolated in addition to calopogonium isoflavone A, jamaicin, durmillone, durallone, 6-methoxycalopogoniumisoflavone A and Tephrosin (Buyinza, 2020 a).

Antiplasmodial results

A total of ten compounds (Figure 3) and three samples of crude extracts were screen against both chloroquine sensitive (D6) and chloroquine resistant (W2) Plasmodium falciparum strains with the common anti-malarial drug chloroquine as the positive control (Table 2).

Table 2: Antiplasmodial results.

S/No.	Name of sample	W2 - IC50s (M±SD) (µg/ml)	D6 - IC50s (M±SD) (µg/ml)
1	Durmillone (13)	141.6±5.8	140.9±15.6
2	Durallone (14)	>160	>160
3	Ichthynone (15)	>160	124.3±17.4
4	Jamaicin (16)	100.4±5.9	>160
5	Barbigerone (17)	79.0±17.5	106.4±19.2
6	Calopogoniumisoflavone-A(18)	139.2±14.5	95.4±13.9
7	Isoerythrine-A-4′-(3-methylbutyl-2-ethyl)ether (19)	>160	122.5±18.9
8	Kaempferol (20)	>160	>160
9	Millettone (21)	132.1±7.4	108.9±26.1
10	Millettosin (22)	87.9±8.9	66.7±30.2
11	Flower extract	113.1±8.2	113.6±26.1
12	Stem bark extract	63.7±8.6	46.1±4.5
13	Seed pod extract	136.9±19.3	158.1±19.9
14	Chloroquine (standard)	121.2±11.0ng/ml	17.9±4.6ng/ml

The crude extract of the stem bark had the highest respective activity of 63.7±8.6 and 46.1±4.5 µg/ml against W2 and D6. The Seed pod extract had the least activities of 136.9±19.3 µg/ml towards W2 and 158.1±19.9 µg/ml against D6. Barbigerone (17) (79.0±17.5) and milletosin (22) (87.9±8.9) were the active compounds against W2 while Calopogoniumisoflavone-A (18) (95.4±13.9 µg/ml) and milletosin (22) (66.7±30.2 µg/ml) were the most active towards D6. From the test results, milletosin (22) was active towards both W2 and D6 with a respective IC50s of 87.9±8.9 and 66.7±30.2 µg/ml.

The most active compounds 17, 18 and 22 are C-6 deoxygenated, a likely indicator that C-6 oxygenation may interfere with activity. Among the C-6 deoxygenated isoflavanoids, 16,17,18 and 19, those with a free methoxyl group at C′-4 (17 and 18) were the most active and activity increased with oxygenation of ring B (17). Meanwhile, 12a oxygenation of rotenoid enhances activity.

Important to note is that two of the most active compounds (18 and 22) were found in the seed pod extract which was the least active of the crude extracts. This means that these compounds have antagonistic activities while in the extract. More still, the acitivity of the pure compounds did not match that of the most active crude extract, an indication that pure compounds in this extract work ssynergistically.

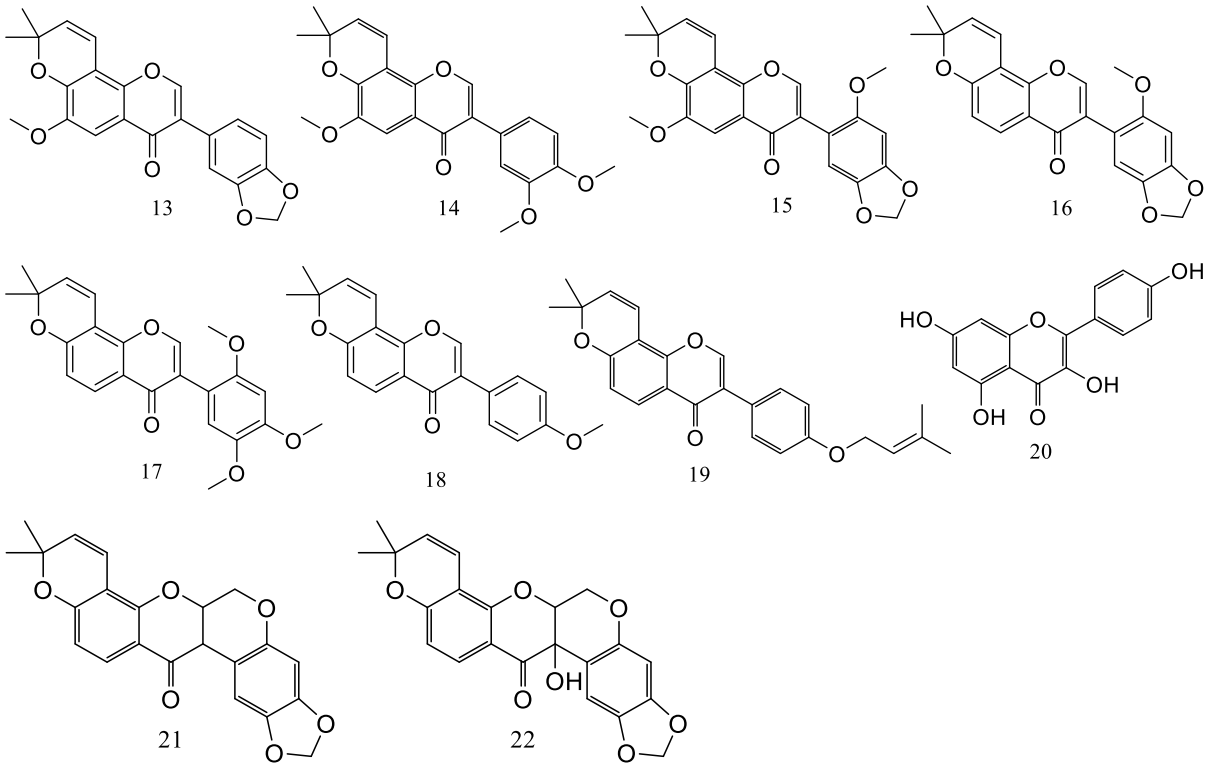


Figure 3: Structure of tested compounds

Limitations

Nature is "mean" producing some of the compounds reservingly, hence could only give amounts just sufficient for spectroscopic studies. Resource constraints limited testing of all the compounds characterized, yet the untasted compounds may be having a better activity than the tested compounds.

Conclusion and Recommendation

The antiplasmodial results show a moderate activity as earlier observed by Derese *et al.*, 2014. Synergistic effect of the compounds with conventional drugs can be sought. Since malaria can cause oxidative stress, and flavonoids are known antioxidants, such compounds as these tested have a double fold activity and are therefore important molecules which must be studied further. The structure activity relationship (SAR) discussed, suggests structural modification on the tested compounds in order to enhance antiplasmodial activity.

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