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TREATMENT AND PROPHYLAXIS - ORIGINAL PAPER

Constituents from ripe figs of *Ficus vallis-choudae* Delile (Moraceae) with antiplasmodial activity

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Abstract

Ripe figs, barks, and wood of *Ficus vallis-choudae* are used in traditional medicine against several conditions including nausea and malaria. However, its use is still to be scientifically documented and validated. Hence, the aim of the present work was to evaluate the antiplasmodial activity of the dichloromethane-methanol (DCM-MeOH (1:1)) crude extract, their hexane, dichloromethane, ethyl acetate, and methanoli fractions, as well as the isolated chemical constituents. The chemical study of the DCM-MeOH (1:1) crude extract of *F. vallis-choudae* figs led to the isolation of fifteen (15) known compounds identified based on their spectroscopic data [one-dimensional (1D) and two-dimensional (2D) nuclear magnetic resonance (NMR), mass spectrometry] and by comparison of these data with those reported in the literature. Some of the isolated compounds were assessed in vitro for their antiplasmodial activity against *Plasmodium falciparum* chloroquine-sensitive 3D7 (*Pf*3D7) and multidrug-resistant Dd2 strains. The dichloromethane fraction exhibited very good antiplasmodial activity against both strains with IC_{50} values of 13.86 µg/mL and 8.18 µg/mL, respectively. Among the tested compounds, wighteone (**2**) was the most active against *P. falciparum* 3D7 ($IC_{50} = 24.6 \pm 1.5$ µM) and Dd2 ($IC_{50} = 11.9 \pm 2.4$ µM) strains. The obtained results could justify the traditional uses of *F. vallis-choudae* against malaria. Wighteone appears to be the most active ingredient. However, further consideration of this compound as starting point for antimalarial drug discovery will depend upon its selectivity of action towards *Plasmodium* parasites.

Highlights

- 15 (fifteen) compounds were isolated from the dichloromethane-methanol extract of *Ficus vallis-choudae.*
- Their structures were determined on the basis of their spectroscopic data.
- The dichloromethane fraction showed promising activities on the *Pf*3D7 and *Pf*Dd2 strains with IC_{50} values of 13.86 and 8.18 µg/mL, respectively.
- Wighteone was the most active compound against *Pf*Dd2 ($IC_{50} = 11.9 \pm 2.4$ µM).

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Introduction

Malaria is an endemic disease in most tropical regions of Africa, Asia, and Latin America and its incidence have been increasing these recent times due to drug resistance and the emergence of the Covid-19 pandemic. An estimated 228 million cases of malaria occurred worldwide in 2018 with the largest burden of morbidity (93%) in Africa (WHO 2019). Chemotherapy remains a key component of malaria control and elimination strategies. Artemisinin-based combination therapy was the most commonly used drug-based therapy between 2010 and 2018 in African public health sectors (WHO 2019), but the high cost and the low availability in rural areas is still an important health problem. The emergence of artemisinin-resistant *Plasmodium falciparum* strains in Africa turned the situation worse (Huayun et al. 2017). Hence, understanding and controlling the spread of antimalarial resistance, particularly to artemisinin and its partner drugs remains a top priority. Therefore, alternative antimalarial drugs need to be developed, and medicinal plants are known as promising sources of potential antimalarial compounds.

The genus *Ficus* (Moraceae) is one of the largest genera of angiosperms with more than 800 species of trees, shrubs, hemiepiphytes, climbers, and creepers in the tropics and subtropics worldwide. It is an important genetic resource due to its high economic and nutritional values and also an important part of the biodiversity in the rainforest ecosystem. *Ficus* species are also a good source of food for fruit-eating animals in tropical areas (Rønsted et al. 2007). *Ficus vallis-choudae* Dellile (synonyms *Ficus schweinfurthii* Miquel) is a shrub or small tree up to 8 m tall. It is distributed in tropical Africa from Senegal to Cameroon, from Sudan to Ethiopia and Malawi (Vivien and Faure 1996). Fruits, bark, and wood are the most used parts of *Ficus vallis-choudae* against several conditions including nausea and malaria (Oliver 1960). Several phytochemical and pharmacological surveys were already done worldwide on different *Ficus* species. However, only a few research studies were conducted on *Ficus vallis-choudae*. Our research group has previously reported the isolation of one ceramide, steroids, and triterpenoids from the methanolic extract of the figs of this plant as well as the α-glucosidase inhibitory activity and DPPH radical scavenging potency (Bankeu et al. 2017). However, to provide scientific validation to the traditional use of this plant to treat malaria, in-depth investigation of stem bark and other parts of *Ficus vallis-choudae* for antiplasmodial was required. In the present article, we report the antiplasmodial activity of the dichloromethane-methanol extract *F. vallis-choudae* figs, its hexane, dichloromethane, ethyl acetate, and methanolic fractions, as well as the isolated chemical constituents.

Materials and methods

General experimental procedures

The used equipments were those reported by Chouna et al (2021). Column chromatography (CC) was performed on silica gel (230–400 mesh). Fractions were monitored by thin-layer chromatography (TLC) using Merck precoated silica gel sheets (60 F_{254}), and the identification of spots on the TLC plate was carried out by spraying with sulfuric acid reagent solution and heating the plate to about 80 °C.

Plant material

The figs of *Ficus vallis-choudae* Dellile were collected in May 2019 at Egona II (Center region of Cameroon). Mr. NANA Victor, botanist at the National Herbarium, Yaoundé, by comparison with the existing voucher specimen No 5115/HNC4, identified the plant material.

Extraction and isolation

The plant material (1.5 kg) was air-dried, pulverized, and extracted three times with 4 L of CH_2Cl_2-MeOH (1:1) mixture at room temperature (24℃) (each time for 24 h). The solvent was evaporated under reduced pressure to afford 119.1 g of crude extract. A part of the extract (118.1 g) was partitioned with *n*-hexane, dichloromethane (DCM), ethyl acetate, and methanol to afford fractions of 72.9, 6.5, 11.1, and 25.6 g, respectively.

The *n*-hexane fraction (FH) was subjected to column chromatography (CC) over silica gel (Merck, 230–400 mesh) eluting with the mixtures of *n*-hexane–EtOAc (1:0 → 0:1) and EtOAc/MeOH (1:0 → 0:1) with increasing polarities. Fractions of 300 mL each were collected and combined according to their TLC profiles to afford five major sub-fractions labeled FH1–FH5. Sub-fraction FH1 (10.5 g) was submitted to CC over silica gel using *n*-hexane–EtOAc (1:0 → 4:6) as solvent systems to yield **7** (50.3 mg) and **8** (55.2 mg). Compound **14** (40 mg) crystallized in sub-fraction FH2 (9.7 g) and was filtered off by simple filtration. Sub-fraction FH3 (13.9 g) was submitted to purified CC over silica gel eluted with *n*-hexane–EtOAc (1:0 → 2:8) to afford compounds **5** (9.2 mg), **4** (8.7 mg), and **11** (25.1 mg). The purification of sub-fraction FH4 (22.8 g) over silica

gel CC using *n*-hexane–EtOAc (1:0 → 2:8) as elution solvents yielded compounds **2** (20.5 mg), **3** (5.4 mg), and **1** (6.9 mg). The sub-fraction FH5 (15.4 g) was subjected to CC with *n*-hexane–EtOAc (6:4 → 0:1) and EtOAc/MeOH (1:0 → 85:15) over silica gel to afford compounds **6** (5 mg) and **15** (30 mg).

Likewise, the DCM fraction (6.5 g) was subjected to the CC over silica gel (Merck, 230–400 mesh) eluting with *n*-hexane–EtOAc (1:0 → 0:1) and EtOAc/MeOH (1:0 → 0:1) systems of increasing polarities. Fractions of 300 mL each were collected and combined according to their TLC profiles to afford four major sub-fractions labeled (FD1–FD4). The sub-fraction FD1 (1.43 g) was further subjected to CC over silica gel and eluted with *n*-hexane–EtOAc (1:0 → 0:1) to afford compound **9** (5.4 mg). Further CC of the sub-fraction FD2 (3.21 g) with *n*-hexane–EtOAc (8:2 → 0:1) afforded compounds **10** (20.8 mg) and **12** (6.2 mg). The sub-fraction FD3 (1.12 g) was subjected to CC over silica gel with *n*-hexane–EtOAc (6:4 → 0:1) to yield compound **13** (15.7 mg).

Physical and spectroscopic data of the isolated compounds

5,7,4′-trihydroxyisoflavone (Genistein) (1): Yellow powder from *n*-hexane–EtOAc (1:1), mp 289–291 °C [Literature (Lit.) 290–292 °C (Mykhailenko et al. 2017)], **^{1}H NMR (CD_3OD, 600 MHz)**: δ_H (ppm) = 8.08 (1H, s, H-2), 7.40 (2H, d, *J* = 8.9 Hz, H-2′/6′), 6.87 (2H, d, *J* = 8.9 Hz, H-3′/5′), 6.37 (1H, d, *J* = 2.2 Hz, H-8), 6.25 (1H, d, *J* = 2.2 Hz, H-6); **^{13}C NMR (CD_3OD, 150 MHz):** δ_C (ppm) = 182.6 (C-4), 166.0 (C-7), 163.9 (C-5), 159.8 (C-9), 158.8 (C-4′), 154.8 (C-2), 131.4 (C-2′/6′), 123.8 (C-3), 123.3 (C-1′), 116.2 (C-3′/5′), 106.3 (C-10), 100.1 (C-6), 94.8 (C-8).

Wighteone (Erythrinin B) (2): Yellow powder from *n*-hexane–EtOAc (4:6), mp 218–220 °C [Lit. 219–220 °C (Kinoshita et al. 1990)], **^{1}H NMR (CD_3OD, 600 MHz):** δ_H (ppm) = 13.03 (1H, s, HO-5), 7.98 (1H, s, H-2), 7.28 (2H, d, *J* = 8.5 Hz, H-2′/6′), 6.74 (1H, d, *J* = 8.5 Hz, H-3′/5′), 6.31 (1H, s, H-8), 5.13 (1H, m, H-2″), 3.21 (2H, d, *J* = 7.3 Hz, H-1″), 1.67 (3H, d, *J* = 1.5 Hz, 5″-CH_3), 1.56 (3H, d, *J* = 1.5 Hz, 4″-CH_3); **^{13}C NMR (CD_3OD, 150 MHz):** δ_C 182.0 (C-4), 163.4 (C-5), 160.4 (C-7), 158.8 (C-4′), 157.3 (C-9), 154.6 (C-2), 132.2 (C-3″), 131.5 (C-2′/6′), 124.3 (C-3), 123.5 (C-2″), 123.4 (C-1′), 116.3 (C-3′/5′), 112.7 (C-6), 106.1 (C-10), 94.0 (C-8), 26.2 (C-4″), 22.4 (C-1″), 18.2 (C-5″).

Lupiwighteone (3): Yellow powder from *n*-hexane–EtOAc (4:6), mp 133–135 °C [Lit. 133–134 °C (Al-Maharik and Botting 2003)], **^{1}H NMR (CD_3OD, 600 MHz)**: δ_H (ppm) = 8.16 (1H, s, H-2), 7.40 (2H, d, *J* = 8.9 Hz, H-2′/6′), 6.87 (2H, d, *J* = 0.8.9.Hz, H-3′/5′), 6.30 (1H, s, H-6), 5.23 (1H, m, H-2″), 3.44 (2H, d, *J* = 7.1 Hz, H-1″), 1.88 (3H, d, s,H-5″), 1.70 (3H, d, s, H-4″); **^{13}C NMR (CD_3OD, 150 MHz):** δ_C (ppm) = 182.6 (C-4), 163.3(C-7), 161.4 (C-5), 158.8 (C-4′), 156.9 (C-9), 154.8 (C-2), 132.4 (C-3″), 131.4 (C-2′/6′), 124.4 (C-1′), 123.4 (C-3), 123.4 (C-2″), 116.2 (C-3′/5′); 107.9 (C-8), 106.3 (C-10), 99.6 (C-6), 25.9 (C-4″), 22.3 (C-1″), 17.9 (C-5″).

Derrone (4): Yellow powder from *n*-hexane–EtOAc (3:7), mp 178–179 °C [Lit. 179–181 °C (Máximo et al. 2002)], **^{1}H NMR ($CDCl_3$, 600 MHz):** δ_H (ppm) = 12.89 (1H, s, HO-5), 7.88 (1H, s, H-2), 7.38 (2H, d, *J* = 8 Hz, H-2′/6′), 6.88 (1H, d, *J* = 8 Hz, H-3′/5′), 6.68 (1H, *J* = 10.0 Hz, H-4″), 6.33 (1H, s, H-6), 5.60 (1H, d, *J* = 10.0 Hz, H-3″), 5.15 (1H, s, HO-4′), 1.48 (6H, s, CH_3); **^{13}C NMR ($CDCl_3$, 150 MHz):** δ_C (ppm) = 181.2 (C-4), 162.4 (C-5), 159.7 (C-7), 156.1 (C-4'), 152.4 (C-9), 130.5 (C-2′/6′), 127.6 (C-3″), 123.8 (C-3), 123.1 (C-1′), 115.8 (C-3′/5′), 114.7 (C-4″), 106.2 (C-10), 100.5 (C-6), 101.3 (C-8), 78.3 (C-2″), 28.4 (C-5″/6″).

Alpinumisoflavone (5): Yellow powder from *n*-hexane–EtOAc (7:3), mp 212–214 °C [Lit. 213–214 °C (Ndemangou et al. 2013)], **^{1}H NMR ($CDCl_3$, 600 MHz):** δ_H (ppm) = 13.18 (1H, s, HO-5), 7.82 (1H, s, H-2), 7.39 (2H, d, *J* = 8 Hz, H-2′/6′), 6.89 (1H, d, *J* = 8 Hz, H-3'/5'), 6.73 (1H, *J* = 10.0 Hz, H-4″), 6.33 (1H, s, H-8), 5.62 (1H, d, *J* = 10.0 Hz, H-3″), 5.15 (1H, s, HO-4′), 1.47 (6H, s, CH_3); **^{13}C NMR ($CDCl_3$, 150 MHz):** δ_C (ppm) = 181.1 (C-4), 159.7 (C-7), 157.5 (C-9), 157.0 (C-5), 156.0 (C-4′), 130.5 (C-2′/6′), 128.4 (C-4″), 123.7 (C-3), 123.3 (C-1′), 115.7 (C-3′/5′), 115.6 (C-3″), 106.3 (C-10), 105.8 (C-6), 96.0 (C-8), 78.2 (C-2″), 28.5 (C-5″/6″).

Oleanolic acid-28-*O*-*β*-D-glucopyranosyl ester (6): white amorphous powder from *n*-hexane–EtOAc (3:7), **^{13}C NMR ($CDCl_3$, 150 MHz): Aglycone:** δ_C (ppm) = 174.5 (C-28), 140.5 (C-13), 122.3 (C-12), 79.7 (C-3), 56.3 (C-5), 50.3 (C-9), 48.0 (C-9), 47.2 (C-19), 46.0 (C-18), 42.5 (C-17/14), 39.0 (C-8), 38.6 (C-4), 38.5 (C-1), 36.9 (C-10), 34.4 (C-21), 34.1 (C-22), 31.9 (C-7), 31.8 (C-29), 29.9 (C-20), 29.1 (C-23), 27.4 (C-2/15), 23.9 (C-27), 22.8 (C-11/16), 21.0 (C-6), 19.8 (C-30), 19.5 (C-26), 14.3 (C-25), 11.8 (C-24), **Glucose:** δ_C (ppm) = 94.0 (C-1′), 76.5 (C-3′), 76.4 (C-5′), 72.2 (C-2′), 69.6 (C-4′), 61.3 (C-6′).

***β*-palmitate (7):** white amorphous powder from *n*-hexane–EtOAc (98:2), **^{13}C NMR ($CDCl_3$, 150 MHz):** δ_C (ppm) = 145.5 (C-13), 121.8 (C-12), 80.7 (C-3), 55.4 (C-5), 47.7 (C-9), 47.4 (C-18), 46.9 (C-19), 41.9 (C-14), 40.0 (C-8), 38.4 (C-1), 37.9 (C-4), 37.8 (C-22), 37.3 (C-10), 34.8 (C-21), 33.5 (C-29), 32.7 (C-17 and C-20), 32.6 (C-7), 28.5 (C-28), 28.2 (C-23), 27.1 (C-2), 26.3 (C-15 and C-16), 26.1 (C-27), 23.8 (C-11 and C-30), 18.4 (C-6), 17.0 (C-26),16.8 (C-24), 15.7 (C-25); **Palmitoyl:** 173.9 (C-1′), 31.2 (C-2′), 29.3–29.9 (C-4′-14′), 25.3 (C-3′), 22.8 (C-15′), 14.3 (C-16′).

***β*-Amiryn acetate (8):** white amorphous powder from *n*-hexane–EtOAc (97:3), **^{13}C NMR ($CDCl_3$, 150 MHz):** δ_C (ppm) = 145.4 (C-13), 121.8 (C-12), 81.1 (C-3), 55.4 (C-5), 47.7 (C-9), 47.4 (C-18), 46.9 (C-19), 41.9 (C-14), 38.4

(C-1), 38.4 (C-4/8), 37.3 (C-22), 37.3 (C-10), 34.8 (C-21), 33.5 (C-29), 32.6 (C-7), 32.7 (C-20), 31.2 (C-17), 28.2 (C-24/28), 27.1 (C-2/16), 26.3 (C-15), 26.1 (C-27), 23.7 (C-30), 23.6 (C-11), 18.4 (C-6), 16.9 (C-26), 16.7 (C-25), 15.7 (C-23); **Acetyl:** 171.2 (C-1′), 21.5 (C-2′).

Capparisides (9): white amorphous powder from *n*-hexane–EtOAc (7:3), **^{1}H NMR (CD_3OD, 600 MHz):** δ_H (ppm) = 7.87 (1H, s, H-2), 2.23 (3H, s, CH_3); **^{13}C RMN (CD_3OD):** δ_C (ppm) = 170.3 (COOH), 151.8 (C-4), 145.8 (C-3), 142.8 (C-5), 140.4 (C-2), 14.8 (CH_3).

5-Hydroxymethylfuran-3-carboxylic acid (10): white powder from *n*-hexane–EtOAc (1:1), mp 144–146 °C **[**Lit. 145–147 °C (Ma et al. 2015)**], ^{1}H NMR (CD_3OD, 600 MHz):** δ_H (ppm) = 7.96 (1H, s, H-2), 6.50 (1H, s, H-4), 4.42 (2H, s, CH_2O); **^{13}C NMR (CD_3OD, 150 MHz):** δ_C (ppm) = 176.9 (COOH), 170.4 (C-5), 147.4 (C-3), 141.0 (C-2), 110.7 (C-4), 61.2 (CH_2OH).

Oleanolic acid (**11**): White crystals from methanol, mp 304–306 °C [Lit. 303.306 °C (Cai and Wu 1996)].

Maslinic acid (12): ^{13}C NMR (CD_3OD, 150 MHz): white amorphous powder from *n*-hexane–EtOAc (1:1), δ_C (ppm) = 180.9 (C-28), 144.8 (C-13), 123.4 (C-12), 84.5 (C-3), 69.5 (C-2), 56.7 (C-5), 48.9 (C-9), 48.1 (C-1), 47.7 (C-17), 47.3 (C-19), 42.9 (C-14), 42.8 (C-18), 40.5 (C-4), 39.3 (C-8/10), 34.6 (C-21), 33.8 (C-22), 33.6 (C-29), 33.9 (C-7), 31.6 (C-20), 29.3 (C-23), 28.8 (C-15), 24.1 (C-11), 24.0 (C-16), 23.7 (C-27/30), 19.6 (C-6), 17.8 (C-26), 17.4 (C-25), 17.1 (C-24).

Erythrinin C (**13**): Yellow cristals from *n*-hexane–EtOAc (7:3), **^{1}H NMR ($CDCl_3$, 150 MHz)**: Yellow amorphous powder, ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H (ppm) = 13.18 (1H, s, 5-OH), 9.64 (1H, s, 4′-OH), 8.10 (1H, s, H-2), 7.38 (2H, d, J = 8.5 Hz, H-2′/6′), 6.84 (2H, d, J = 8.5 Hz, H-3′/5′), 6.43 (1H, s, H-8), 4.81 (2H, m, H-2″), 3.10 (2H, d, J = 8.5 Hz, H-3″), 1.31 (3H, s, H-6″), 1.26 (3H, s, H-5″); **^{13}C NMR (DMSO-d_6, 100 MHz)**: δ_C (ppm) = 182.3 (C-4), 168.1 (C-7), 159.5 (C-5), 158.7 (C-9), 157.9 (C-4′), 93.1 (C-2″), 154.9 (C-2), 131.4 (C-2′/6′), 124.8 (C-3), 123.1 (C-1′), 116.1 (C-3′/5′), 110.8 (C-6), 107.1 (C-10), 89.9 (C-8), 72.2 (C-4″), 27.4 (C-3″), 25.3 (C-6″), 23.5 (C-5″).

***β*-Sitosterol** (**14**): White crystals from methanol, mp: 134–135 °C [Lit. 136–137 °C (Sen et al. 2012)].

***β*-Sitosterol-3-*O*-*β*-D-glucopyranoside** (**15**): White crystals from methanol, mp: 290−292 °C [Lit. 290−291 °C (Wang et al. 2009)].

Antiplasmodial assay

Chloroquine-sensitive (*Pf*3D7) and multidrug-resistant (*Pf*Dd2) strains of *P. falciparum* were continuously cultured as reported by Chouna et al. (2021). The previously SYBR green I-based fluorescence method described by Smilkstein et al. (2004) was used to evaluate the antiplasmodial activity. The growth inhibition percentage for each test sample was determined using Microsoft Excel and data analysis was performed with GraphPad Prism 5.0 fitting by non-linear regression and dose–response curves were drawn to determine the inhibitory concentration that reduces parasite viability by 50% (IC_{50}).

The degree of resistance was determined by comparison of the antiplasmodial IC_{50} of inhibitors on the chloroquine-sensitive and multi-resistant strains of *P. falciparum* using the following formula:

RI = IC_{50} multidrug-resistant strain/IC_{50} chloroquine-sensitive strain.

Results and discussion

Phytochemical analysis

The dichloromethane-methanol (1:1) crude extract of the figs of *Ficus vallis-choudae* was repeatedly subjected to silica gel column chromatography (CC) to yield fifteen compounds identified as 5,7,4′-trihydroxyisoflavone (**1**) (Sordon et al. 2017); wighteone (**2**) (Kinoshita et al. 1990); lupiwighteone (**3**) (Al-Maharik and Botting 2003); derrone (**4**) (Máximo et al. 2002); alpinumisoflavone (**5**) (Rahman et al. 2007; El-Masry et al. 2002); oleanolic acid-28-*O*-*β*-D-glucopyranosyl ester (**6**) (Young et al. 1997); *β*-amyrin palmitate (**7**) (Bankeu et al. 2017); *β*-amyrin acetate (**8**) (Du et al. 2003; Okoye et al. 2014); cappariside (**9**) (Yang et al. 2010); 5-hydroxymethylfuran-3-carboxylic acid (**10**) (Evidente et al. 2009); maslinic acid (**12**) (Tanaka et al. 2003); erythrinin C (**13**) (Chen et al. 2019). The remaining compounds were identified by co-TLC with authentic samples and melting points measurement as oleanolic acid (**11**) (Cai and Wu 1996), *β*-sitosterol (**14**) (Sen et al. 2012), and 3-*O*-*β*-D-glucopyranoside of *β*-sitosterol (**15**) (Wang et al. 2009) (Fig. 1). The isolation of isoflavonoids, triterpenes, and steroids is in agreement with the previous results obtained from *Ficus* species (Bankeu et al. 2011, 2017; Fongang et al. 2015).

Antiplasmodial activity

The crude extract, fractions, and isolated compounds were assessed in vitro for their antiplasmodial activity against chloroquine-sensitive (*Pf*3D7) and multidrug-resistant (*Pf*Dd2) strains of *P. falciparum*. Out of the tested fractions, the dichloromethane fraction (FVFD) exhibited good antiplasmodial activities on the *Pf*3D7 and *Pf*Dd2 with IC_{50} values of 13.86 and 8.18 µg/mL, respectively (Table 1). Four compounds (**9, 10, 12, 13**) were isolated through its repeated purification. The multi-targeted activity of maslinic acid (**12**) as an antimalarial natural compound was previously demonstrated (Moneriz et al. 2011), and might justify the activity observed for FVFD. However, the low amount of

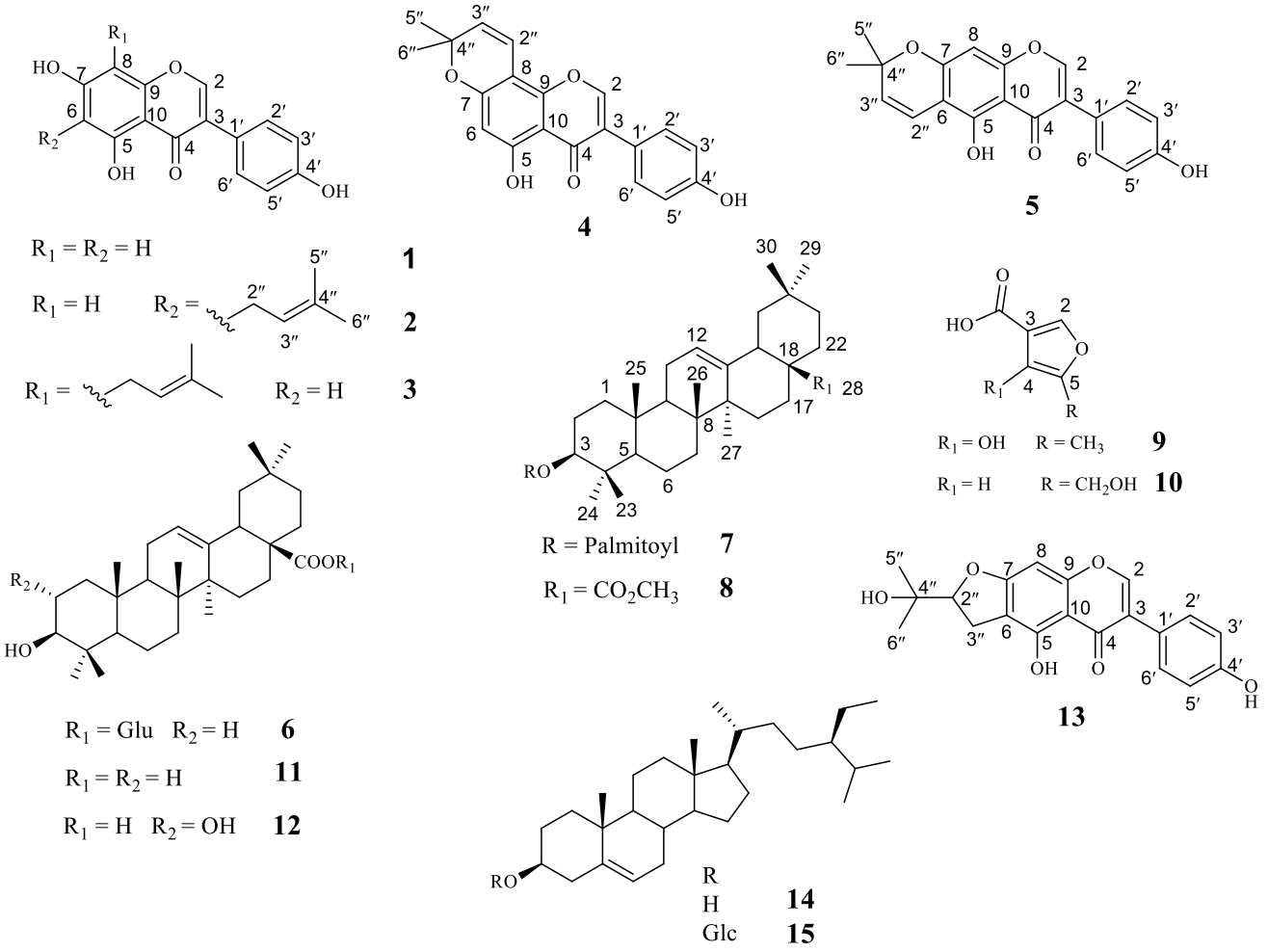

Fig. 1 Sructures of compounds **1**–**15**

12 isolated in this work did not allow the evaluation of its antiplasmodial activity against both *P. falciparum* strains. Compound **2** (wighteone) was the most active against *Pf*Dd2 ($IC_{50} = 11.9 \pm 2.4$ µM) and *Pf*3D7 ($IC_{50} = 24.6 \pm 1.5$ µM). However, a recent report indicated that wighteone inhibits cell proliferation, suppressed EGFR signalling pathway, caused cell cycle redistribution and induced cell apoptosis, and could provide a novel potential therapeutic strategy for NSCLC patients with T790M mutation (Sun et al. 2021). For further consideration of this compound (**2**) as starting point for antimalarial drug discovery, cytotoxicity assessment using normal mammalian cells is required. The main structural difference between **1** and **2** is the presence of a prenyl group at C-6 of **2**, thus suggesting that the prenyl moiety may contribute to the high activity of **2**. This result corroborates previous findings as prenyl moiety including isoflavonoids have been reported to considerably increase various biological activities such as antiplamodial, antifungal, and anticancer potencies of secondary metabolites (Zelefack et al. 2012; Yang et al. 2015). These results could support the traditional use of *Ficus vallis-choudae* for the treatment of malaria. Wighteone, maslinic acid, and genistein may be eventually qualified as antiplasmodial active principles of this medicinal plant.

Conclusion

Fifteen (15) known compounds including six isoflavonoids, five triterpenoids, two steroids, and two furan derivatives were isolated from the dichloromethane-methanol (1:1) crude extract of *Ficus vallis-choudae* figs. This is the first report of the isolation of these compounds (excepted **7**, **11,** and **14**) from *Ficus vallis-choudae*. The dichloromethane fraction showed promising activities on the *Pf*3D7 and *Pf*Dd2 strains with IC_{50} values of 13.86 and 8.18 µg/mL, respectively. Wighteone was the most active against *Pf*Dd2 ($IC_{50} = 11.9 \pm 2.4$ µM) and *Pf*3D7 ($IC_{50} = 24.6 \pm 1.5$ µM).

Table 1 Antiplasmodial activity of compounds and fractions from the dichloromethane-methanolic extract of *F. vallis-choudae*

	Codes	*Pf*3D7 $IC_{50} \pm SD^*$ (µg/mL)	*Pf*Dd2 $IC_{50} \pm SD^*$ (µg/mL)	Resistance index (RI)
Extract	FVDMe	74.3 ± 3.3	15.9 ± 0.02	0.21
Fractions	FVFH	74.8 ± 2.5	60.6 ± 0.1	0.80
	FVFD	13.9 ± 0.2	8.2 ± 2.1	0.59
	FVFEA	47.6 ± 3.6	28.6 ± 0.2	0.60
	FVFMe	˃25	7.5 ± 1.3	-
Compounds	N0	$IC_{50} \pm SD^*$ (µM)	$IC_{50} \pm SD^*$ (µM)	
	1	˃36	˃36	0.99
	2	24.6 ± 1.5	11.9 ± 2.4	0.48
	4	˃36	˃36	-
	5	˃36	˃36	-
	6	˃36	˃36	-
	7	˃36	19.5 ± 2.9	-
	8	˃36	˃36	-
	10	˃36	˃36	-
Positive control (µM)	Chloroquine	0.057 ± 0.006	0.43 ± 0.04	
	Artemisinin	0.023 ± 0.002	0.012 ± 0.001	

*Samples were tested in triplicate against *P. falciparum* in culture; data points are means ± standard deviation (SD); *FV*, *Ficus vallis-choudae; FVDMe*, dichloomethane-methanol crude extract of FV; *FVFH*, hexane fraction of FV; *FVFD*, dichloromethane fraction of FV; *FVFEA*, ethyl acetate fraction of FV; *FVFMe*, methanolic fraction of FV

Wighteone and maslinic acid might be suggested as the backbone of the antiplasmodial potency of *Ficus vallis-choudae*. However, their safety towards normal mammalian cells should be demonstrated.

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Declarations

Competing interest The authors declare no competing interests.

References

Al-Maharik N, Botting NP (2003) Synthesis of lupiwighteone via a para-Claisen–Cope rearrangement. Tetrahedron 59(23):4177–4181. https://doi.org/10.1016/S0040-4020(03)00579-9

Bankeu JJK, Dawé A, Mbiantcha M, Feuya TGR, Ali I, Tchuenmogne TMA, Lateef M, Lenta BN, Muhammad SA, Ngouela AS (2017) Characterization of bioactive compounds from *Ficus vallis-choudae* delile (Moraceae). Trends Phytochem Res 1(4):235–242

Bankeu JJK, Khayala R, Lenta BN, Noungoué DT, Ngouela SA, Mustafa SA, Asaad K, Choudhary MI, Prigge ST, Hasanov R, Nkengfack AE, Tsamo E, Ali MS (2011) Isoflvone dimers and other bioactive constituents from the figs of *Ficus mucuso*. J Nat Prod 74(6):1370–1378. https://doi.org/10.1021/np100896w

Cai L, Wu CD (1996) Compounds from *Syzygium aromaticum* possessing growth inhibitory activity against oral pathogens. J Nat Prod 59(10):987-990. https://doi.org/10.1021/np960451q

Chen H, Qian Y, Zhao X, Lv T, Wang B, Gong GS, Qiu X, Luo L, Zhang M, Qin GW, Khaskheli MI, Yang C, (2019) Compounds from the root of *Pueraria peduncularis* (Grah. ex Benth.) Benth. and their antitumor effects. Nat Prod Com 14(12):1–6. https://doi.org/10.1177/1934578X19882521

Chouna HSD, Bankeu JJK, Fongang YSF, Dize D, Ponou BK, Bitchagno GTM, Awantu AF, Lenta BN, Fekam FB, Ngouela SA, Opatz T, Sewald N (2021) Constituents of *Peperomia vulcanica* Baker & C. H. Wright (Piperaceae) with antiparasitic activity. Phytochem Lett 41:14–20. https://doi.org/10.1016/j.phytol.2020.10.010

Du J, He ZD, Jiang RW, Ye WC, Xu HX, But PP (2003) Antiviral flavonoids from the root bark of *Morus alba* L. Phytochemistry 62(8):1235–1238. https://doi.org/10.1016/s0031-9422(02)00753-7

El-Masry S, Amer EM, Abdel-Kader SM, Zaatout HH (2002) Prenylated flavonoids of *Erythrina lysistemon* grown in Egypt. Phytochemistry 60(8):783–787. https://doi.org/10.1016/s0031-9422(02)00202-9

Evidente A, Cristinzio G, Punzo B, Andolfi A, Testa A, Melck D (2009) Flufuran, an antifungal 3,5-disubstituted furan produced by *Aspergillus flavus* Link. Chem Biodivers 6(3):328–334. https://doi.org/10.1002/cbdv.200800292

Fongang YSF, Bankeu JJK, Ali MS, Awantu AF, Zeeshan A, Assob CN, Mehreen L, Lenta BN, Ngouela SA, Tsamo E (2015)

Flavonoids and other bioactive constituents from *Ficus thonningii* Blume (Moraceae). Phytochem Lett 11:139–145. https://doi.org/10.1016/j.phytol.2014.11.012

Huayun Z, Guoding Z, Jianxia T, Yaobao L, Weiming W, Yuanyuan C, Sui X, Yaping G, Julin L, Chao Z, Qi G, Didier M, Arnab P, Haitao Y, Qingfeng Z, Jun C (2017) Emergence of indigenous artemisinin-resistant *Plasmodium falciparum* in Africa. N Engl J Med 376(10):991–993. https://doi.org/10.1056/NEJMc1612765

Kinoshita T, Ichinose K, Takahashi C, Ho FC, Wu JB, Sankawa U (1990) Chemical studies on *Sophora tomentosa*: the isolation of a new class of isoflavonoid. Chem Pharm Bull 38(10):2756–2759. https://doi.org/10.1248/cpb.38.2756

Ma Y-M, Ma C-C, Li T, Wang J (2015) A new furan derivative from an endophytic *Aspergillus flavus* of *Cephalotaxus fortunei*. Nat Prod Res 30(1):79–84. https://doi.org/10.1080/14786419.2015.1038262

Máximo P, Lourenço A, Feio SS, Roseiro JC (2002) A new prenyl isoflavone from *Ulex jussiaei*. Z Naturforsch C 57(7–8):609–613. https://doi.org/10.1515/znc-2002-7-810

Moneriz C, Mestres J, Bautista JM, Diez A, Puyet A (2011) Multi-targeted activity of maslinic acid as an antimalarial natural compound. FEBS J 278(16):2951–2961. https://doi.org/10.1111/j.1742-4658.2011.08220.x

Mykhailenko O, Kovalyov V, Kovalyov S, Krechun A (2017) Isoflavonoids from the rhizomes of *Iris hungarica* and antibacterial activity of the dry rhizomes extract. Ars Pharm 58(1):39–45. https://doi.org/10.4321/S2340-98942017000100005

Ndemangou B, Sielinou VT, Vardamides JC, Ali MS, Lateef M, Iqbal L, Afza N, Nkengfack AE (2013) Urease inhibitory isoflavonoids from different parts of *Calopogonium mucunoides* (Fabaceae). J Enzyme Inhib Med Chem 28:1156–1161

Okoye NN, Ajaghaku DL, Okeke HN, Ilodigwe EE, Nworu CS, Okoye FBC (2014) Beta-amyrin and alpha-amyrin acetate isolated from the stem bark of *Alstonia boonei* display profound anti-inflammatory activity. Pharm Biol 52(11):1478–1486. https://doi.org/10.3109/13880209.2014.898078

Oliver B (1960) Medicinal plants in Nigeria. Nigerian College of Arts and Science, Lagos, Nigeria

Rahman MZ, Sultana SJ, Faroque CF, Ferdous F, Rahman MS, Islam MS, Rashid MA (2007) Phytochemical and biological investigation of *Erythrina variegate*. Saudi Pharm J 15(2):140–145

Rønsted N, Salvo G, Savolainen V (2007) Biogeographical and phylogenetic origins of African fig species (*Ficus* section *Galoglychia*). Mol Phylogenetics Evol 43(1):190–201. https://doi.org/10.1016/j.ympev.2006.12.010

Sen A, Dhavan P, Shukla KK, Singh S, Tejovathi G (2012) Analysis of IR, NMR and antimicrobial activity of β-sitosterol isolated from *Momordica charantia*. Sci Secure J Biotech 1(1):9-13

Smilkstein M, Sriwilaijaroen N, Kelly JX, Wilairat P, Riscoe M (2004) Simple and inexpensive fluorescence-based technique for high-throughput antimalarial drug screening. Antimicrob Agents Chemother 48(5):1803–1806. https://doi.org/10.1128/AAC.48.5.1803-1806.2004

Sordon S, Popłoński J, Tronina T, Huszcza E (2017) Microbial glycosylation of daidzein, genistein and biochanin A: two new glucosides of biochanin A. Molecules 22(1):81–89. https://doi.org/10.3390/molecules22010081

Sun P, Qu Y, Wang Y, Wang J, Wang X, Sheng J (2021) Wighteone exhibits an antitumor effect against EGFR L858R/T790M mutation non-small cell lung cancer. J Cancer 12(13):3900–3908. https://doi.org/10.7150/jca.54574

Tanaka JCA, Vidotti GJ, Da Silva CC (2003) A new tormentic acid derivative from *Luehea divaricata* Mart. (Tiliaceae). J Braz Chem Soc 14(3), 475–478

Vivien J, Faure JJ (1996) Fruitiers sauvages d'Afrique espèces du Cameroun. Nguila-Kerou (Eds.), France, p. 416

Wang Y, Lai D, Zhang Y, Kang A, Cao Y, Sun W (2009) Study of steroidal saponins in *Dioscorea zingiberensis* C.H. Wright. J Nat Products (India) 2, 123-132.

World Health Organization (2019) World malaria report 2019.

Yang T, Wang C, Liu H, Chou G, Cheng X, Wang Z (2010) A new antioxidant compound from *Capparis spinosa*. Pharm Biol 48(5):589–594. https://doi.org/10.3109/13880200903214231

Yang X, Jiang Y, Yang J, He J, Sun J, Chen F, Zhang M, Yang B (2015) Prenylated flavonoids, promising nutraceuticals with impressive biological activities. Trends Food Sci Technol 44(1):93–104. https://doi.org/10.1016/j.tifs.2015.03.007

Young MCM, Potomati A, Chu EP, Haraguchi M, Yamamoto M, Kawano T (1997) ^{13}C NMR analysis of monodesmosidic saponins from *Gomphrena macrocephala*. Phytochemistry 46(7):1267–1270. https://doi.org/10.1016/S0031-9422(97)80024-6

Zelefack F, Guilet D, Valentin A, Fongang RCS, Kom B, Chevalley S, Ngouela SA, Tsamo E, Fabre N, Dijoux-Franca M-G (2012) Antiplasmodial and cytotoxic activities of flavonoids and arylbenzofuran derivatives from *Morus mesozygia*. Greener J Biol Sci 2(2):20–24

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