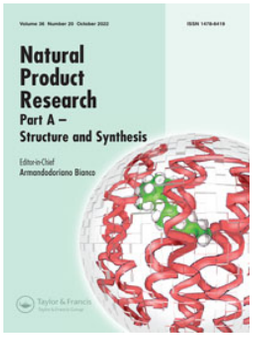

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A novel pentacyclic triterpene acid from the stem barks of *Combretum fragrans* F. Hoffm (Combretaceae)

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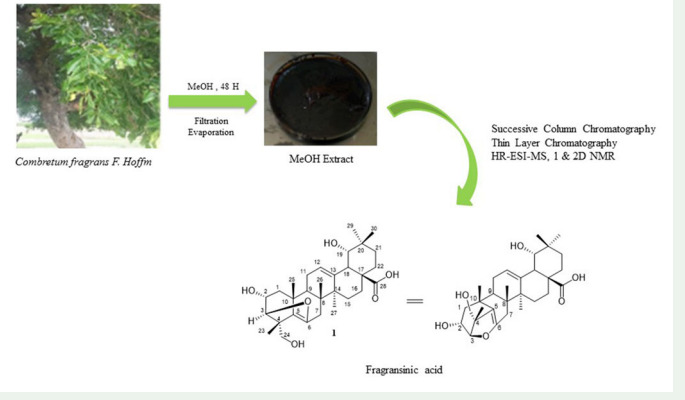
ABSTRACT

A phytochemical study was carried out on stem bark of *Combretum fragrans* F. Hoffm., a medicinal plant belonging to the Combretaceae family and used traditionally in the treatment of various ailments. Column chromatography separation on silica gel of the crude methanol extract from stem barks of *C. fragrans* led to the isolation of a new pentacyclic triterpene acid, with a 3,6-epoxide bridge and trivially named as fragransinic acid (1), along with four known compounds: betulin (2), betulinic acid (3), bellericagenin B (4) and a mixture of β-sitosterol (5) and stigmasterol (6). Structures were elucidated by extensive spectroscopic analyses including 1D and 2D NMR, mass spectrometry as well as by comparison with literature data. The above compounds were isolated for the first time from *C. adenogonium*. Implications for chemosystematics and traditional medicine were briefly discussed.



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1. Introduction

Combretaceae are a large family of plants with about 600 species regrouped into 20 genera (McGaw et al. 2001). While *Combretum* and *Terminalia* are the most common genera within the Combretaceae family, the *Combretum* genus comprises about 200–250 species, distributed throughout the tropics and subtropics. However, it is absent from Australia and the Pacific Island (Roy et al. 2014). Species of *Combretum* genus are well known in African traditional medicine, and used for the treatment of a variety of ailments and diseases including microbial infections, mental problems, scorpion and snake bites, heart and worm remedies and fever (Atindehou et al. 2004). Previous pharmacological studies showed that species from *Combretum* genus possess several bioactivities including antibacterial (Njume et al. 2011), antifungal (Masoko et al. 2007), anti-inflammatory and analgesic activity (Ojewole 2008), cytotoxic and antioxydant (Nopsiri et al. 2014) as well as antidiabetic activity (Chika and Bello 2010). Phytochemical studies of the genus delivered various secondary metabolites including flavonoids, triterpenes, lignans, phenanthrenes and stilbenoids (Lima et al. 2012; Roy et al. 2014). *Combretum adenogonium* ex A. Rich., synonym *Combretum fragrans* F. Hoffm., is a medicinal plant belonging to the *Glabripetala* section of *Combretum* genus (Maurin et al. 2010). It is a shrub or a small tree which grows up to 10–12 m high. The plant is found in deciduous woodland, wooded grassland associated with seasonally waterlogged clay soils and on shallow, stony soils (Wickens 1973). *C. fragrans* is used in African folk medicine for the treatment of various types of diseases like coughs, syphilis, leprosy, septic wounds, fungal infection of the scalp, diarrhea, hypertension, incurable wound, malaria, snake bite, gonorrhea, pain and inflammation (Maregesi et al. 2007; Maima et al. 2008; Mbiantcha et al. 2018). Pharmacological investigation of *C. fragrans* extracts has been established to have antibacterial, antifungal and antiproliferative properties (Fyhrquist et al. 2006; Maregesi et al. 2008; Gade et al. 2021), while phytochemical analysis of leaves, stem bark and roots has revealed the presence of flavonoids, triterpenes, sterols, saponins and tannins (Chhabra and Uiso 1990; Dawe et al. 2016; Gade et al. 2021). Despite the well-documented benefits of *C. fragrans*, only few phytochemical studies have been done on it. The present study aims to isolate bioactive compounds from *C. fragrans* stem bark. We described here the isolation and structural elucidation of compounds **1**–**6** identified for the first time from this plant species.

2. Results and discussion

A total of 1 kg of air-dried powder of the stem bark of *C. fragrans* was extracted by maceration in methanol (3 L) to afford 40 g of crude extract. A quantity of that extract was separated by column chromatography on silica gel and led to the isolation of a novel pentacyclic triterpene acid, fragransinic acid (**1**) together with five known triterpenoids, betulin (**2**), betulinic acid (**3**), bellericagenin B (**4**) and a mixture of β-sitosterol (**5**) and stigmasterol (**6**) (Figure 1).

Compound **1** was obtained as an amorphous powder by column chromatography on silica gel with *n*-hexane/ethyl acetate (70:30 v/v). It showed an m.p of 298–299 °C and gave positive Liebermann–Bürchard test, suggesting a triterpene skeleton. The

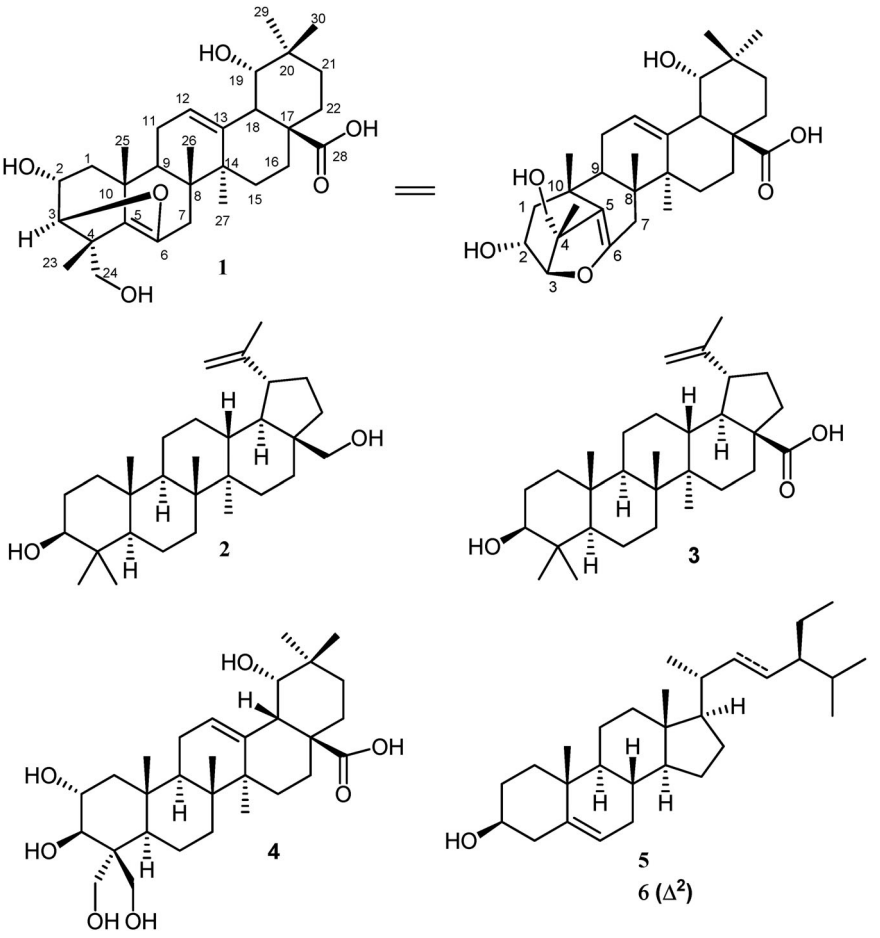

Figure 1. Structures of triterpenoids identified in *C. fragrans*.

(+)-ESI-HRMS spectrum (Figure S1a) of compound **1** showed a pseudomolecular ion peak, $[M + Na]^+$ at *m/z* 523.3017 (calc. 523.3030) corresponding to the molecular formula $C_{30}H_{44}O_6Na^+$ and implying nine degrees of unsaturation. The ^{1}H-NMR spectrum (Figure S2) of compound **1** displayed signals attributable to six methyl angular functions in the high field region of the spectrum, at δ 0.86 (3H, s), 0.96 (3H, s), 0.99 (3H, s), 1.21 (3H, s), 1.29 (3H, s) and 1.30 (3H, s). One olefinic proton as triplet at δ 5.41 characteristic of a proton in H-12 position of the olean-12-ene triterpene skeleton (Mahato and Kundu 1994), three oxymethine protons at 3.25 (1H, *d*, *J* = 9.4 Hz, H-3), 3.77 (1H, *dddd*, *J* = 11.5 Hz, 9.5 Hz and 4.2 Hz, H-2) and 3.30 (1H, *d*, *J* = 3.9 Hz, H-19); two signals of diastereotopic oxymethylene protons at 4.08 (1H, *d*, *J* = 8.8 Hz) and 4.18 (1H, *d*, *J* = 8.8 Hz) were also observed. The data reported above are similar to those of bellericagenin B (Mahato et al. 1992), a known pentacyclic triterpene isolated from the same plant. However, compound **1** differs from bellericagenin B by the absence of a hydroxyl group on its carbon C-23, the presence of a double bond between carbons C-5 and C-6, and by the epoxy bridge formed between C-3 and C-6 carbons. The ^{13}C NMR spectrum (Figure S3) of compound **1** showed signals of olefinic carbons C-12

and C-13 of the olean-12-ene skeleton and at δ 122.8 and 142.6, respectively (Mahato and Kundu 1994). Moreover, one sp^2 carbon of carboxylic acid function at δ 180.7 was assigned to C-28. A joint analysis of the ^{13}C NMR spectrum with DEPT and HSQC spectra displayed three oxymethine carbons at δ 68.4 (C-2), 83.2 (C-3) and 81.0 (C-19); one oxymethylene carbon at δ 84.3 (C-24) as well as two additional quaternary olefinic carbons at δ 115.0 (C-6) and 150.3 (C-5). The ^{1}H-^{1}H COSY spectrum (Figure S5) showed a correlation between H-2 at δ 3.77 and H-3 at δ 3.25, and H-1a/b at δ 2.02/1.06; A correlation between H-18 at δ 3.11 and H-19 at δ 3.30 as well as a correlation between H-24a at δ 4.18 and H-24b at 4.08. We also observed a correlation of H-12 at δ 5.41 and two diastereotopic methylene protons H-11a/b at δ 2.23/2.09. The HMBC spectrum (Figure S6) showed a strong correlation between H-3 (δ 3.25) and carbons C-2 (δ 68.4), C-23 (δ 20.7) and C-24 (δ 84.3). The spectrum also displayed correlations of H-24a/b (δ 4.18/4.08) and carbons at δ 83.2 (C-3), δ 115.0 (C-5) and δ 150.3 (C-6). We also observed an important HMBC correlation between two diastereotopic protons H-7a/b (δ 2.23/1.54) and carbons at δ 150.3 (C-5) and δ 115.0 (C-6). Other HMBC correlations (Figure S15) were observed between a methyl proton at δ 1.21 (Me-25) and carbon at δ 150.3 (C-5); the methyl at δ 1.30 (Me-27) and carbon at δ 142.6; the methyls at δ 0.96 (Me-29), 0.99 (Me-30) and carbon at δ 81.0 (C-19). Above HMBC correlations allowed us to locate the double bond at δ 150 and 115 between carbons C-5 and C-6 respectively. Compound **1** implies nine degrees of unsaturation while the very close structure to **1,** bellericagenin B, has seven degrees of unsaturation. The additional two degrees of unsaturation in compound **1**, when compared to bellericagenin B, are due to the already established presence of one double bond and most certainly to the presence of an additional ring. The latter is suggested to be resealed between the carbons C-3 and C-6 regarding their chemical shift by forming an 3,6-epoxy bridge, and the absence of the H-6 proton. The coupling constant between the proton H-2β ($J = 11.5$) and H-3α ($J = 11.5$) suggest a *trans* configuration and allowed us to established the 3,6-epoxy bridge to display β-configuration. The complete assignment of ^{1}H and ^{13}C of compound **1** is given in Table S1 and the trivial name fragransinic acid was given to **1**.

The structures of the known compounds were determined by comparison of their spectroscopic data with those from the literature and identified as a mixture of β-sitosterol (**5**) and stigmasterol (**6**) (Nyemb et al. 2018), betulin (**2**) (Prachayasittikul et al. 2010), betulinic acid (**3**) (Ogunmoye et al. 2017) and bellericagenin B (**4**) (Mahato et al. 1992). Notably, all compounds (Figure **1**) are reported for the first time from this plant species.

It should be noted that the presence of triterpenoids may represent a good rationale for ethnomedicinal use, due to the action of betulinic acid (**3**) against the HIV-1 reverse transcriptase (Esposito et al. 2013), in addition to the effectiveness of betulin (**2**), betulinic acid (**3**) and β-sitosterol (**5**) against cancer (Eiznhamer and Xu 2004; Soica et al. 2012; Rauf et al. 2016).

For what concerns the chemosystematic relevance of these triterpenoids only the presence of bellericagenin B (**4**) and the new epoxy-derivative (**1**) fragransinic acid deserve interest. In fact, while bellericagenin B (**4**) had been previously only identified from *Terminalia bellerica* (Mahato et al. 1992) and thus may prove its taxonomical

value at the genus level within the plant family of Combretaceae, the new epoxy-derivative fragransinic acid (**1**) may be endowed of chemosystematic relevance at the species level.

3. Experimental

3.1. General experimental procedures

The melting point of the new compound was recorded in an open capillary using Electrothermal 9100 and is uncorrected. The ^{1}H and ^{13}C NMR data were recorded on a Bruker Avance AV-500 and 600 spectrometers with tetramethylsilane (TMS) as standard. Chemical shifts are given in ppm (δ) and the coupling constant (J) in Hz. ESI-MS spectra were registered on a QTOF Spectrometer (Bruker, Germany) equipped with a ZQ F1 source and was operated in positive mode (scan: 150–1500 *m/z*, centroid CV = 20). Column chromatography (CC) was performed on silica gel 60 (70–230 mesh, Merck), and thin layer chromatography (TLC) was performed on silica gel precoated plates F-254 Merck (20 × 20 cm). Spots were visualized under UV light (254 and 365 nm), sprayed with 5% of phosphomolybdic acid prepared in ethanol, then heated.

3.2. Plant material

Stem bark of *Combretum fragrans* F. Hoffm were collected during the month of May 2017 at Padarmé located in Bibémi subdivision, in the North Region of Cameroon. The sample was identified at the National Herbarium of Cameroon where a voucher specimen is deposited under the number 39753/HNC.

3.3. Extraction and isolation

A quantity of 1 kg of air-dried powder from the stem bark of *C. fragrans* was extracted by maceration in 5 L of methanol for 48 h. After filtration, the resulting solution was evaporated under reduced pressure using a rotary evaporator. Extraction was repeated three times to afford 40 g of methanol crude extract. A portion of 30 g of the extract was column chromatographed on silica gel and eluted with a gradient of *n*-hexane-ethyl acetate followed by ethyl acetate-methanol. Separation led to the isolation of four pure compounds **1**–**4** and one mixture **5** + **6**.

Fragransinic acid (**1**): white amorphous powder; m.p. 298–299 °C; (+)-ESI-HRMS *m/z* 523.3017 $[M+Na]^{+}$; ESI-MS(+) *m/z* 501.7 $[M+H]^{+}$ and 523.7 $[M+Na]^{+}$; ^{1}H-NMR (CD_3OD, 600 MHz): δ 2.02 (1H, m, Ha-1), 1.06 (1H, m, Hb-1), 3.77 (1H, dddd, J = 11.5, 9.5 and 4.2 Hz, H-2), 3.25 (1H, d, J = 9.4 Hz, H-3), 2.23 (1H, d, J = 17.6 Hz, Ha-7), 1.54 (1H, d, J = 17.6 Hz, Hb-7), 1.96 (1H, t, J = 9.1 Hz, H-9), 2.23 (1H, m, Ha-11), 2.09 (1H, m, Hb-11), 5.41 (1H, t, H-12), 2.37 (1H, m, Ha-15), 1.63 (1H, m, Hb-15), 1.80 (1H, m, Ha-16) 1.03 (1H, m, Hb-16), 3.11 (1H, s, H-18), 3.30 (1H, d, J = 3.9 Hz, H-19), 1.78 (1H, m, Ha-21) 1.64 (1H, m, Hb-21), 1.29 (3H, s, Me-23), 4.08 (1H, d, J = 8.8 Hz, Ha-24) 4.18 (1H d, J = 8,8 Hz, Hb-24), 1.21 (3H, s, Me-25), 0.86 (3H, s, Me-26), 1.30 (3H, s, Me-27), 0.96 (3H, s, Me-29) and 0.99 (3H, s, Me-30); ^{13}C-NMR (CD_3OD, 151 MHz): δ 49.8 (C-1), 68.4 (C-2), 83.2 (C-3), 49.5 (C-4), 115.0 (C-5), 150.3 (C-6), 29.9 (C-7), 40.5 (C-8), 44.6 (C-9), 46.3 (C-

10), 22.7 (C-11), 122.8 (C-12), 142.6 (C-13), 41.0 (C-14), 26.8 (C-15), 27.7 (C-16), 45.1 (C-17), 43.1 (C-18), 81.0 (C-19), 34.6 (C-20), 32.5 (C-21), 27.9 (C-22), 20.7 (C-23), 84.3 (C-24), 20.5 (C-25), 17.7 (C-26), 23.8 (C-27), 180.0 (C-28), 27.3 (C-29) and 23.5 (C-30).

4. Conclusion

The phytochemical study of the methanol crude extract from the stem bark of *C. fragrans* F. Hoffm led to the isolation of a new pentacyclic triterpenic acid (**1**) and five known compounds (**2**–**6**). The structures of compounds were elucidated by extensive spectroscopic analysis. Compounds **1**–**6** are recognized for the first time from *Combretum fragrans*. The presence of bellericagenin B (**4**), which was previously only isolated from *Terminalia bellerica* (Combretaceae), is reported here and may in future serve to indicate the Combretaceae family, genus *Terminalia* or *Combretum*. Notably, the new compound fragransinic acid (**1**), structurally closely related to compound **4**, may serve as taxonomic marker of the species *Combretum fragrans*.

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