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Ficusanolide A and ficusanolide B, two new cinnamic acid derivative stereoisomers and other constituents of the stem barks of *Ficus exasperata* Vahl. (Moraceae)

Stevine Claudiale Popwo Tameye [a,*], Ahri Bernie Djamen Mbeunkeu [a], Yannick Fouokeng [a], Nathalie Samantha Jouwa Tameye [b,c], Georges Bellier Tabekoueng [a,c], Jean Duplex Wansi [a], Norbert Sewald [c], Jean Claude Ndom [a], Anatole Guy Blaise Azebaze [a,*]

[a] Laboratory of Chemistry, Department of Chemistry, Faculty of Science, University of Douala, P.O. Box 24157, Douala, Cameroon
[b] Department of Organic Chemistry, Faculty of Science, University of Yaounde I, P.O. Box 812, Yaounde, Cameroon
[c] Organic and Bioorganic Chemistry, Faculty of Chemistry, Bielefeld University, Bielefeld, D-33501, Germany

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ABSTRACT

Phytochemical investigation of the stem barks of *Ficus exasperata* Vahl. (Moraceae) led to the isolation of two new cinnamic acid derivatives stereoisomers, named ficusanolide A (**1**) and ficusanolide B (**2**) along with twelve known compounds: ficusanol (**3**), umbelliferone-6-carboxylic acid (**4**), oxypeucedanin hydrate (**5**), marmesin (**6**), decursinol (**7**), *β*-amyrin acetate (**8**), lupeol (**9**), betulinic acid (**10**), ursolic acid (**11**), a mixture of stigmasterol (**12**) and *β*-sitosterol (**13**), sitosteryl-3-*O*-*β*-*D*-glucopyranoside (**14**); and one hemisynthetic derivative : per acetylated betulinic acid (**15**). Their structures were established by the means of their physical data (melting point, rotatory power), their spectroscopic data, particularly IR, NMR (^{1}H, ^{13}C, DEPT, COSY, HSQC and HMBC) data, and HR-ESIMS data. Crude extract, compounds **1**, **2**, **3**, **5**, **6**, **7**, **9**, **10**, **11**, as well as the semisynthetic derivative **15** were evaluated for their cytotoxic activity on the human cervix carcinoma cell line KB-3−1 and the human colon cancer cell line HT-29. Ursolic acid **11** showed a moderate activity on both cancer cells tested with IC_{50s} of 50.9 μM and 34.4 μM respectively.

1. Introduction

Ficus exasperata Vahl. belongs to the Moraceae family, a family of flowering plants with about 40 genera and more than 1400 species of which over 1000 species are members of the genus *Ficus* (Aubreville, 1954; Berg et al., 1985). It is a terrestrial tropical shrub or tree that grows up to about 20 m in height. This plant prefers evergreen and secondary forest habitats and is widely distributed from Mozambique, Zambia and northern Angola to Senegal and Ethiopia including central Africa (Berg and Wiebes, 1992). It is popularly known as “sand paper tree” due to the scabrous surface of the leaves, which makes it to find use domestically as abrasive for polishing hard surfaces such as wood, metal, or ivory articles like kitchen utensils, gourds, sticks, bowls, spear shafts, chairs and bracelets. The wood is used for making canoes, houses, pots wood, furniture, stools, utensils, containers and drums, and is also used as fuel wood for making charcoal (Ijeh and Ukweni, 2007; Kar, 2007; Amponsah et al., 2013; Mouho et al., 2018).

Ficus exasperata is widely used in traditional medicine. The roots are used for the treatment of urinary tract infection, gonorrhea, asthma, tuberculosis, cough, eye problems and worm expellant. The stem is used for leprosy, wounds, sores, abscesses and stomach ache (Sonibare et al., 2006). Sap from the bark is used to stop bleeding. The stem bark is locally applied on the body for the treatment of malaria (Uzama et al., 2018). The plant is also used for the treatment of dysentery, jaundice, rash, fungal infection, itching, oedema, ringworm, rheumatism, lumbar and intercostal pain. It is also used for the treatment of ulcer, hypertension, mouth wash against thrush, inflammation of the gums and other mouth and throat ailments, headache, tumors and typhoid fever (Odunbaku et al., 2008).

The phytochemical screening of the methanol crude extracts from the leaves, stem barks and roots of *Ficus exasperata* revealed the presence of alkaloids, flavonoids, saponins, phenols and tannins (Ijeh and

* Corresponding authors.
E-mail addresses: claudialepopwo@yahoo.fr (S.C. Popwo Tameye), azebaze@yahoo.com (A.G.B. Azebaze).

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Ukweni, 2007; Kofie et al., 2015; Uzama et al., 2018). Previous phytochemical investigation of the stem bark of *F. exasperata* reported the isolation of a new sphingolipid and furanocoumarins and also fatty acids, glycerol esters, glycerol derivatives, pheophorbide/pheophytin derivatives, flavonoid and pyrimidine derivatives (Jiofack et al., 2012; Bafor et al., 2013; Amponsah et al., 2013). A recent work on the methanol extract of the roots of *F. exasperata* permitted the isolation of a new cinnamic acid derivative (Popwo et al., 2020). In the continuity of this work, we report the isolation and structural elucidation of two new cinnamic acid derivatives along with twelve known compounds from the stem barks of *Ficus exasperata*.

2. Results and discussion

2.1. Phytochemical study

The methanol extract of the air-dried stem barks of *Ficus exasperata* was chromatographed on a column of silica gel and thin layer chromatography (TLC) eluted with ether petroleum, the mixture of ether petroleum and EtOAc and mixture of EtOAc and MeOH in increasing polarity to afford two new cinnamic acid derivatives stereoisomers together with twelve known compounds (see Fig. S20 Supplementary informations). By comparison to the reported data, the known compounds were identified as ficusanol (**3**) (Popwo et al., 2020), umbelliferone-6-carboxylic acid (**4**) (Hyun et al., 2013), oxypeucedanin hydrate (**5**) (Jiofack et al., 2012), marmesin (**6**) (Monteiro et al., 2002), decursinol (**7**) (Mo et al., 2017), β-amyrin acetate (**8**), lupeol (**9**), betulinic acid (**10**) (Chandramu et al., 2003), ursolic acid (**11**) (Martins et al., 2013), a mixture of stigmasterol (**12**) and β-sitosterol (**13**), and sitosteryl-3-*O*-β-*D*-glucopyranoside (**14**) (Habib et al., 2007).

The acetylation of betulinic acid was carried out by using acetic anhydride and pyridine at room temperature for 12 h to afford 3-*O*-acetyl-betulinic acid (**15**) (Fadipe et al., 2017).

Compound **1** and compound **2** were obtained as a pale-yellow amorphous powder and gave the same molecular formula of $C_{15}H_{17}O_4N$. The Fourier Transform (FT)-IR spectrum of compound **1** displayed prominent absorptions at 3411 (OH), 1647 (amide carbonyl), 1584 (C═C) and 1538 (CN) cm^{-}—^{1}. Their UV spectrum in methanol displayed two absorption maxima at λ_{max} 235.0 and 263.0 nm consistent with n→л* and л→л* electronic transitions typical of chromophore having double bonds and heteroatoms. The ^{1}H-NMR spectrum shows in the olefinic region the signals of two *trans* coupled protons deshielded by conjugation to a carbonyl at δ_H 6.40 (d, J =16.0 Hz) and 7.79 (d, J =16.0 Hz). In addition, it also displayed the signals of two olefinic proton of a six-member ring which were correlated on the COSY spectrum, typical of a chromene ring at δ_H 5.54 (d, J =10.0 Hz) and 6.45 (d, J =10.0 Hz) (Cheng-Hsiung et al., 1989) alongside two aromatic protons appearing as singlet at δ_H 7.21 and 6.50 suggestive of the presence of a 2,3,5,6-tetrasubstituted benzene ring. This ^{1}H-NMR spectrum indicates the presence of one methoxy group at δ_H 3.86 (s) in addition of a hydroxymethylene group at δ_H 3.64 (d, J =11.8 Hz) and 3.60 (d, J =11.8 Hz). Its ^{13}C NMR spectrum shows the signal of 15 carbon atoms including one α,β-unsaturated amid carbonyl at δ_C 172.0 (C-1′) attached on the benzene ring as evidenced by ^{3}J HMBC correlations with the olefinic proton H-3′ (δ_H 7.79) and between proton H-3′ with aromatic carbon C-7(δ_C 161.1). The observed ^{13}C chemical shift of C-4′ (68.7) and C-7 (161.1) are consistent with the deshielding effect of oxygen substitution more electro-attractive than nitrogen atom to confirm that the amino group is at C-1′. Indeed, the amino group at position 4′ would have caused the decrease of the chemical shift of C-4′ under 60 ppm and at position 7, it would have caused the decrease of the chemical shift of C-7 under 150 ppm. In addition, HMBC correlation of the methoxy group with aromatic carbon C-7 indicates its position at C-7 on the aromatic ring. HMBC spectrum also shows strong correlations between the angular olefinic carbon of the chromene ring at δ_C 126.1 (C-3) indicating the presence of a 2-methyl-2-hydroxymethylenechromene moiety. The ether bond between C-2/C-9 was further confirm with the absence of ^{3}J heteronuclear correlation between oxymethylene protons H-4′ and the quaternary aromatic carbon C-9. Taking into account of biosynthesis consideration of chromene which derive from C-alkylation of phenol derivative by dimethylallyl pyrophosphate to form a C-alkylated intermediate, followed by an oxidative cyclization of the alkyl group to form chromene. The structure of compound **1** was thus determined as 3′-[(2-hydroxymethyl)-7-methoxy-2-methyl-2*H*-6-chromenyl]-(*E*)-acrylamid and the trivial name of ficusanolide A was given.

NMR spectra data of both compound **1** and **2** were quite superposable with a slight difference observed on the coupling constant of the olefinic protons H-2′ (5.87, d, J =12.3 Hz) and H-3′ (6.89, d, J =12.3 Hz) indicating that both compounds were stereoisomers. Indeed, compound **2** exhibited a coupling constant of 12.3 Hz suggestive of a *cis* configuration of the double bond while it was *trans* (J =16.0 Hz) in compound **1**. The structure of compound **2** was thus determined as 3′-[(2-hydroxymethyl)-7-methoxy-2-methyl-2*H*-6-chromenyl]-(*Z*)-acrylamid with the trivial name of ficusanolide B (Figs. 1 and 2)

2.2. Biological test

2.2.1. Cytotoxicity

The cytotoxicity of ursolic acid (**11**), lupeol (**9**), betulinic acid (**10**), the per acetylated derivative of betulinic acid (**15**), oxypeucedanin hydrate (**5**), decursinol (**7**), marmesin (**6**), ficusanol (**3**), ficusanolide A (**1**) and ficusanolide B (**2**) was evaluated on two cancers cell lines: The human cervix carcinoma cell line KB-3−1 and the human colon cancer cell line HT-29 at the concentration of 0.00025 mol/L. The results revealed that only ursolic acid exhibited a moderated activity on both tested cancer cells with IC_{50} = 50.9 μM for the human cervix carcinoma cell line KB-3−1 and IC_{50} = 34.4 μM for the human colon cancer cell line HT-29 while the IC_{50} of griseofulvin used as reference was 17 μM and 21 μM respectively (see Table S2 supplementary datas) (Table 1)

3. Experimental

3.1. General experimental procedures

The ^{1}H and ^{13}C NMR spectra were recorded at room temperature using a Bruker DRX-500, 600 MHz spectrometer (Bruker, Rheinstetten, Germany) with TMS as the internal standard (δ 0.00 ppm). The chemical shift values were expressed in ppm units relative to TMS and coupling constants J were measured in Hz. ESI-Mass spectra were obtained with Agilent 6220 TOF LCMS mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). Silica gel 70–230 mesh (Merck) was used for column chromatography, while aluminum sheets precoated with silica gel 60 F_{254} (Merck) were used for TLC with a mixture of ether petroleum-ethyl acetate and ethyl acetate-methanol as eluents. The compounds were visualized under ultraviolet light (254 nm) or by iodine vapor and by spraying with H_2O-H_2SO_4 (1:1) reagents followed by heating.

3.2. Plant material

The stem barks of *F. exasperata* were collected on February 2017 near the campus of the Faculty of Science of the University Douala, Littoral region of Cameroon, with the localisation 4°02′53″N, 9°42′15″E. The plant was identified by Mr. Nana Victor from the National Herbarium of Cameroon by comparison with a deposited specimen registered under the reference number 45,226 HNC.

3.3. Extraction and purification

The stem barks of *F. exasperata* were harvested, chopped into small pieces, air-dried and ground into powder. The obtained powder (4.5 kg) was macerated twice at room temperature using methanol (15 L) for

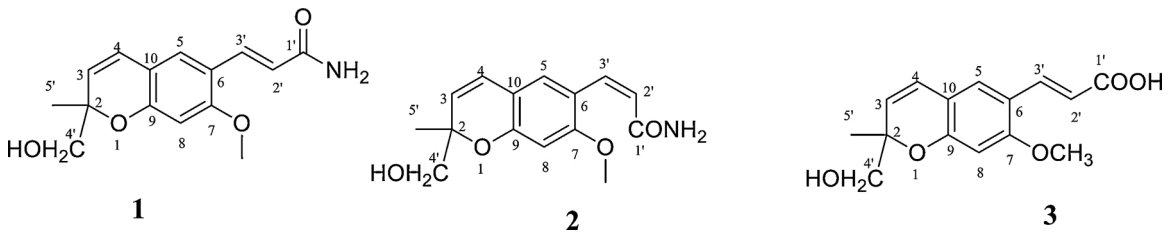

Fig. 1. Structures of compounds **1-3.**

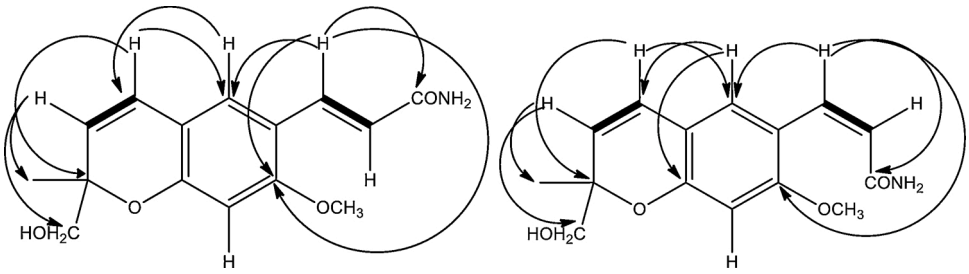

Fig. 2. Some correlations of ficusanolide A and ficusanolide B: HMBC ⌒ COSY ▬.

Table 1
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR assignments for ficusanolide A (1) and ficusanolide B (2) in CD_3OD.

	1			2		
	δ_C	δ_H (m, *J* in Hz)	HMBC	δ_C	δ_H (m, *J* in Hz)	HMBC
2	81.2	–		80.8	–	
3	126.1	5.54 (d, *J* = 10.0)	5′,4′, 10	126.1	5.51 (d, *J* = 10.0)	5′,4′, 10
4	124.4	6.45 (d, *J* = 10.0)	2, 5, 9	124.4	6.39 (d, *J* = 10.0)	2, 5, 9
5	127.5	7.21 (s)	3′, 4, 7, 9	127.5	7.30 (s)	3′, 4, 7, 9
6	118.8	–		118.8	–	
7	161.1	–		160.1	–	
8	100.8	6.50 (s)	6, 10	100.8	6.45 (s)	6, 10
9	157.6	–		157.6	–	
10	117.5	–		117.8	–	
1’	172.0	–	–	172.7	–	–
2’	115.5	6.40 (d, *J* = 16.0)	6, 1′	115.5	5.87 (d, *J* = 12.3)	6, 1′
3’	137.9	7.79 (d, *J* = 16.1)	1′, 7	137.9	6.89 (d, *J* = 12.3)	1′, 7
4’	68.7	3.60 (d, J = 11.8) 3.64 (d, J = 11.8)	5′, 3	68.6	3.62 (d, J = 11.8) 3.69 (d, J = 11.8)	5′, 3
5’	23.4	1.38 (s)	3, 4′	23.4	1.36 (s)	3, 4′
MeO	56.2	3.86 (s)		56.1	3.86 (s)	

48H. The resulting mixture was filtrated and the solvent was removed by evaporation under reduced pressure using a rotary evaporator to yield 74.5 g of methanol crude extract.

The methanol crude extract (64.5 g) was chromatographed over a silica gel column, eluting with ether petroleum, a gradient of ether petroleum-EtOAc from 95.5:0.5 to 0:100 (v/v), EtOAc, a gradient of EtOAc-methanol in increasing polarity up to 9:1 (v/v) and finally with methanol. 100 mL of each sub-fractions were collected and pooled on the basis of their TLC profile into 13 fractions (F1-F13).

Fraction F2 eluted with PEET/EtOAc (39:1 to 19:1) yielded **8** (10.8 mg). Fraction F3 eluted with PEET/EtOAc (37:3 to 9:1) afforded **9** (21.5 mg) and the mixture of **12** and **13** (50.6 mg). Elution with PEET/EtOAc (4:2) led to fraction F4, which yielded **10** (55.3 mg) and **3** (2.1 mg). Fraction F6 eluted with PEET/EtOAc (7:3) yielding **11** (15.6 mg) and **5** (6.9 mg). The elution with PEET/EtOAc (3:2) gave fraction F8, which afforded **7** (20.1 mg). Fraction F9 eluted with PEET/EtOAc (3:2 to 1:1) afforded **6** (25.4 mg). Elution with PEET/EtOAc (2:3 to 1:3) led to fraction F10, which yielded **14** (600.0 mg). Fraction F11 eluted with EtOAc gave **1** (6.2 mg) and **2** (4.0 mg). The elution with EtOAc/MeOH (39:1) gave fraction F12, which afforded **4** (20.1 mg).

3.3.1. Preparation of 3-O-acetyl-betulinic acid

A mixture of betulinic acid (0.044 mmol), acetic anhydride (0.021 mol) and pyridine (2 mL) was stirred at room temperature for 12 h. After stopping stirring, the mixture was then transferred into distilled water and partitioned with dichloromethane. This dichloromethane concentrated was thereafter dried and packed into a small column eluted with ethyl acetate: hexane (1:9) ratio to afford acetylated derivative of betulinic acid as a white amorphous powder (0.024 mmol, 54.94 %).

3.4. Cytotoxic assay

The human cervix carcinoma cell line KB-3−1 and the human colon cancer cell line HT-29 were cultivated as a monolayer in DMEM (Dulbecco’s modified Eagle medium) with glucose (4.5 $g.L^{-1}$), L-glutamine, sodium pyruvate and phenol red, supplemented with 10 % foetal bovine serum (FBS) at 37 ℃ in humidified incubators in an atmosphere of 5% CO_2. On the day before the test, the cells (70 % confluence) were detached with trypsin-ethylenediamine tetraacetic acid (EDTA) solution (0.05 %; 0.02 % PBS) and placed in sterile 96-well plates in a density of 10 000 cells in 100 μL medium per well. The dilution series of the compounds were prepared from stock solutions in DMSO of concentrations of 1 mM or 10 mM. The stock solutions were diluted with culture medium (10 % FBS) at least 50 times. Some culture medium was added to the wells to adjust the volume of the wells to the wanted dilution factor. The dilution prepared from stock solution was added to the wells. Each concentration was tested in six replicates. Dilution series were prepared by pipetting liquid from well to well. The control contained the same concentration of DMSO as the first dilution. After incubation for 72 h at 37 °C and 5.3 % CO_2^- humidified air, 30 μL of an aqueous resazurin solution (175 μM) was added to each well. The cells were incubated at the same conditions for 6 h. Subsequently, the fluorescence was measured. The excitation was effected at a wavelength of 530 nm, whereas the emission was recorded at a wavelength of 588 nm. The IC_{50} values were calculated as a sigmoidal dose response curve using GRAPHPAD PRISM 4.03. The IC_{50s} values equal the drug concentrations,

at which vitality is 50 %.

3.5. Ficusanolide A (1)

Pale yellow amorphous powder; $[\alpha]_D^{20}$: +25 (c = 0.35; MeOH) - IR (KBr): νmax 3315.0, 2943.8, 2832.0, 1666.5, 1017.4 and 688.0 cm^{-1}; UV (MeOH) λ_{max} 235.0 nm and 263.0 nm; ^1H (600 MHz; CD_3OD) and ^{13}C (150 MHz, CD_3OD) NMR data, see Table 3; (+)-ESI HRMS *m/z* = 298.1050 $[M + Na]^+$ for $C_{15}H_{17}O_4N$

3.6. Ficusanolide B (2)

Pale yellow amorphous powder; $[\alpha]_D^{20}$: -6,8 (c = 0.36; MeOH) IR (KBr): νmax 3315.0, 2943.8, 2832.0, 1666.5, 1017.4 and 688.0 cm^{-1}; UV (MeOH) λ_{max} 235.0 nm and 263.0 nm ; ^1H (600 MHz; CD_3OD) and ^{13}C (150 MHz, CD_3OD) NMR data, see Table 3; (+)-ESI HRMS *m/z* = 298.1050 $[M + Na]^+$ for $C_{15}H_{17}O_4N$

4. Concluding remarks

In this paper, the phytochemical investigation of methanol extract of the stem barks of *F. exasperata* have been reported and it led to the isolation and structural elucidation of two new cinnamic acid derivative stereoisomers ficusanolide A and ficusanolide B, as well as twelve known compounds by the means of usual spectroscopic methods. Cytotoxic activity was also carried out on some isolated compound.

Declaration of Competing Interest

The authors declare no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phytol.2021.03.027.

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