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**A NEW SULFONYL GLUCOSIDE EUGENOL AND ANTIOXIDANT
PHENOLIC COMPOUNDS FROM *LANNEA ACIDA* AND *LANNEA
WELWITSCHII***

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ABSTRACT

A new unusual eugenyl-*O*- β -*D*-(6'-sulphonylglucopyranoside) and 17 polyphenols have been isolated from the leaves of *Lannea acida* and *Lannea welwitschii*. The structures of the compounds were established using NMR and HR-ESI-MS spectroscopic analysis. Six compounds namely myricetin 3-*O*- β -*D*-arabinofuranoside **1**, myricetin-3-*O*- β -*D*-glucuronic acid **2**, myricetin-3-*O*- β -*D*-xylofuranoside **3**, myricetin **4**, mearnsetin **5**, myricetin-3-*O*- β -*D*-galactopyranoside **6**, were isolated from *L. welwitschii*. Twelve others including the new eugenyl-*O*- β -*D*-(6'-sulphonylglucoside) **7**, myricetin-3-(6''-galloylgalactoside) **8**, quercetin-3-*O*- β -*D*-glucuronic acid **9**, quercetin-3-*O*- β -*D*-glucopyranoside **10**, (-)-epigallocatechin-3-gallate **11**, (-)-epicatechin-3-gallate **12**, myricetin-3-*O*- α -*L*-rhamnopyranoside **13**, myricetin-3-*O*- β -*D*-glucopyranoside **14**, 3,4,5-trigalloylquinic acid **15** and (-)-epigallocatechin **16**, quercetin-3-(6''-galloylglucopyranoside) **17** and (-)-epicatechin **18** were obtained from *Lannea acida*. The antioxidant activity of **2**, **4**, **5**, **10**, **11**, **12**, **13**, **14**, **17** and **18** were evaluated by the DPPH (2, 2'-diphenyl-1-picrylhydrazyl) free radical-scavenging and CUPRAC method. Others due to their inadequate quantities were not evaluated. Compound **18** (IC₅₀ 7.8 \pm 0.1 μ g / mL), **4** (IC₅₀ 18.6 \pm 4.5 μ g / mL), **2** (IC₅₀ 20.0 \pm 0.1 μ g / mL) and **13** (IC₅₀ 20.0 \pm 0.9 μ g / mL) showed better activity than the controls, ascorbic acid (IC₅₀ 23.17 \pm 2.02) and quercetin (IC₅₀ 31.67 \pm 2.88 μ g / mL). This is the first report of the isolation of eugenyl-*O*- β -*D*-(6'-sulphonylglucopyranoside). The seventeen (17) known compounds were reported for the first time in *L. welwitschii* and *L. acida*. Future studies would involve the anti-inflammatory and anticancer activities of these compounds.

Keywords: *L. welwitschii*, *L. acida*, antioxidant activity.

INTRODUCTION

The genus *Lannea* belongs to the family Anacardiaceae and consists of 77 genera with 600 species.^[1] Most of them are used to treat several ailments such as ulcers, enteritis, diarrhea, dysentery, malaria, toothaches, blood pressure and rheumatism.^[2, 3] Some species of *lannea* genus have shown anticancer activity.^[4, 5, 6] The chemical investigation of *lannea* genus has led to identification and isolation of various secondary metabolites, including: carbohydrates, alkylphenols, alkylhexanones, flavonoids, tannins; saponins steroid^[6, 7, 8, 9] and sesquiterpenoids from essential oils.^[10]

Lannea welwitschii (Hiern) Engl. is a tropical tree widely distributed in Ivory Coast. The stem bark is used to treat abdominal pain and skin ulcer and is also used to manage diabetes mellitus in Ghana.^[11] The leaf extract of *Lannea welwitschii* was active against *T. b. brucei*.^[12] Two alkylhydroquinones were isolated from the organic extract of *Lannea welwitschii*.^[13]

Lannea acida A. Rich (fam. Anacardiaceae) is a deciduous tree with a dense rounded crown that usually grows from 1.5 to 10 meters tall. It is found widely distributed in Western tropical Africa, spanning from Senegal to Nigeria.^[14] Preclinical data showed *Lannea acida* to be effective against diarrhea, stomach pains rheumatism and gonorrhea.^[15] Recently demonstrated it was report to have uterotonic effects.^[16] In Ivory Coast, it is used in traditional medicine (NCA laboratory) in combination with other plants to treat cancer.

Due to the ethnomedicinal importance of the 2 *lannea* species in Ivory Coast, this study aimed at exploring the phytochemistry of the 2 and also evaluate the antioxydant activity of the isolated compounds.

MATERIAL AND METHODS

Plant material

Leaves of *L. welwitschii* and *L. acida* were collected in November 2018 at Flakièdougou (Bondoukou) in the East region of Ivory Coast. The plants were identified at the floristic center of university Felix Houphouët Boigny (Abidjan, Ivory Coast), where voucher specimens with numbers: ref. Number UCJ 000982 (for *L. welwitschii*) and ref. Number UCJ 000961 (for *L. acida*) were kept.

General experimental procedure

NMR experiments were carried out in MeOH-*d*₄ on Bruker Avance DRX III 500 instruments. HR-ESI-MS experiments were performed using a Micromass Q-TOF micro instrument. Analytical TLC was performed on pre-coated silica-gel 60 F₂₅₄ Merck and spots were observed under UV light at 254 and 365 nm or visualized by spraying the dried plates with 50% H₂SO₄, followed by heating. CC was carried out on Kieselgel 60 (63-200 mesh). Extracts were fractionned first on vaccumm liquid chromatography (VLC) or dianion HP-20 resin. HPLC was performed on a Dionex apparatus equipped with an ASI-100 autosampler, an Ultimate 3000 pump, a diode array detector UVD 340S and Chromeleon software. Interchim column (C₁₈ - HQ, 5 µm, 250 x 10 mm) was used for semi-preparative HPLC or preparative HPLC (PLC)

with binary gradient eluent (H₂O (filtered at 0.22 with TFA); CH₃CN) and a flow rate of 4 mL/min in semi-preparative HPLC and 20 mL/min in PLC ; the chromatogram was monitored at 205, 210, 254 and 365 nm.

Extraction and isolation

Lannea welwitschii

Coarsely powdered leaves (1.5 Kg) of *L. welwitschii* was exhaustively extracted successively with DCM (15 L) and methanol (15 L). The methanolic extract was dissolved in H₂O (500 mL) and the mixture serially extracted with cyclohexan (2×250 mL), ethyl acetate (2×500 mL), and n-butanol (4×500 mL). The fractions were dried under low temperature and pressure to obtain 0.2962 g of cyclohexan, 2.7295 g of EtOAc and 25.3581 g of n-BuOH fractions. The butanol fraction was separated on VLC C-18 (10 cm x 5 cm) eluting with water/methanol gradient to yield 6 fractions (VLC-1 to VLC-6). Thin-layer chromatography monitoring of these fractions revealed the presence of flavonoids.

Fraction VLC-3 (3.0334 g) was subjected to flash chromatography on normal silica with ethyl acetate, acetone and water (90/10/0; 80/10/10; 60/30/10) which gave 16 fractions.

Fraction 2 (10 mg) was purified using preparative PLC with H₂O/acetonitrile (CH₃CN) (15 to 70% of CH₃CN) as the mobile phase to afford compounds **3** (Rt 7.48 min, 1.4 mg) and **6** (Rt 8.20 min, 2 mg).

Fractions 4 and 5 together (68.8 mg) was purified on semi-prep HPLC eluted with H₂O/ CH₃CN gradient to give compounds **4** (Rt 10.40 min, 1.4 mg) and **5** (Rt 12.38, 1.9 mg).

Fractions 6 and 7 combination (180.7 mg) was run on prep HPLC with C18 column and water/acetonitrile mobile phase (5-100%) to yield a yellowish crystalline compound **1** (Rt 7.81 min, 4.7 mg).

Fraction 15 (23.34 mg) was purified on preparative PLC eluted with H₂O/CH₃CN (15 to 70% of CH₃CN) to yield compound **2** (Rt 8.76 min, 13 mg).

Lannea acida

About 1.5 Kg of coarsely powdered *L. acida* leaves was serially extracted with ethyl acetate (15 L) and 20 % methanol (15 L). The concentrated hydromethanolic extract (94.5 g) was dissolved in H₂O (500 mL) and the solution successively extracted with ethyl acetate (4×500 mL) and n-butanol (4×500 mL).

The butanol fraction (31.7 g) was chromatographed on HP-20 (8 cm x 62 cm) with water-methanol gradient mobile phase. This gave five bulk extracts: Bu1 (8.7 g), Bu2 (5.6 g), Bu3 (9.3 g), Bu4 (6 g) and Bu5 (1.1 g). Extract Bu4 (6 g) was chromatographed on normal silica gel with varying compositions of dichloromethane/methanol/water to yield 12 fractions. Fraction 7, 72.5 mg was purified on preparative PLC with 20 to 70% CH₃CN gradient to yield the new compound **7** (Rt 19.19 min; 3.6 mg). Fraction 5 (715.9 mg) was fractionated on preparative HPLC (C18) eluted with 15 to 35% CH₃CN gradient to give yellowish crystalline substances **13** (Rt 19.50 min, 8 mg) and **14** (Rt 20.34 min, 8 mg).

The residual aqueous extract (33.6173 g) was fractionated on VLC-C₁₈ (10 cm x 5 cm) with water-methanol gradient to give fractions Aq1, Aq2 and Aq3. Fraction Aq2 (4 g) was subjected to flash chromatography on normal silica with dichloromethane/ methanol /water (95/5/0; 70/30/0; 70/30/5; 60/40/7) gradient to give 13 fractions. Fraction 10 (126.1 mg) was purified on preparative PLC using the mobile phase 15-30% CH₃CN gradient to afford **9** (Rt 16.02 min; 2 mg). Fraction 12 (104.5 mg) was purified on preparative PLC, eluting with 15 -70% CH₃CN gradient to yield **15** (Rt 5.50 min; 11.7 mg).

The ethyl acetate extract (8 g) was fractionated on silica with the mobile phase dichloromethane/Methanol (90/10; 0/100) to give six fractions. Fraction 1 (135 mg) was purified on preparative PLC with Water/ CH₃CN as the mobile phase to afford **18** (Rt 19.12 min; 4.4 mg).

Fraction 2 (373.3 mg) was similarly purified as fraction 1 to furnish **16** (Rt 10.03 min; 1 mg), **11** (Rt 19.39 min; 3.9 mg) **17** (Rt 27.04 min; 2 mg) and **12** (Rt 30.22 min; 7.3 mg).

Fraction 3 (1400 mg), on the other hand, was chromatographed on HPLC preparative (C18) eluted with Water / CH₃CN 15 to 35% of CH₃CN to give **8** (Rt 13.05 min; 5.9 mg) and **10** (Rt min; 4.5 mg)

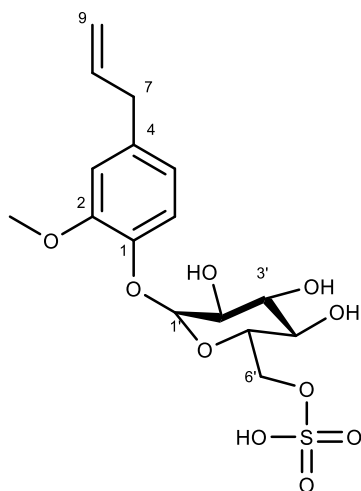


Figure 1 : Eugenyl-*O*- β -*D*-(6'-sulphonylglucopyranoside)

Eugenyl-*O*- β -*D*-(6'-sulphonylglucopyranoside) (**7**), brown amorphous powder. $[\alpha]_D^{20}$ – 4.71 (c 0.857, MeOH). UV (MeOH) λ_{\max} 203 (1.434), 278 (0.266), IR ν^{KBr} , cm^{-1} : 1456, 1508, 1602, 2356 and 3278. ^1H - and ^{13}C -NMR (CD_3OD): Table 1. HR-ESI-MS $[\text{M}-\text{H}]$: 405.0856 (calcd for $\text{C}_{16}\text{H}_{21}\text{O}_9\text{S}$, 405.0855).

Antioxidant assay

DPPH free radical scavenging

The DPPH scavenging activity of some of the isolated compounds was investigated by spectrophotometric methodology.^[17] Briefly, 5 μL of either the standard or sample solutions (dissolved in DMSO) was mixed with 95 μL of DPPH solution (158 μM , dissolved in absolute EtOH). After mixing gently and incubating for 30 min at 37°C, the optical density was measured at λ 515 nm. The percentage of absorbance inhibition at λ 515 nm was calculated using the following equation: % inhibition $[(\text{Abcontrol} - \text{Absample})/\text{Abcontrol}] \times 100$. DPPH solution in EtOH was used as a control. The curve of the % scavenging activity against the concentration of sample was prepared by the MS Excel based program to obtain the IC₅₀. All the tests were conducted in triplicate. The experimental data were expressed as mean \pm standard deviation.

Cupric ion reducing (CUPRAC) method

The cupric ion reducing activity (CUPRAC) was determined according to Ceylan method.^[18] Sample solution (0.5 mL) was added to premixed reaction mixture containing CuCl_2 (1 mL, 10 mM), neocuproine (1 mL, 7.5 mM) and NH_4Ac buffer (1 mL, 1 M, pH 7.0). Similarly, a blank

was prepared by adding sample solution (0.5 mL) to premixed reaction mixture (3 mL) without CuCl₂. Then, the absorbance of the sample and blank was read at 450 nm after 30 min incubation at room temperature. The absorbance of the blank was subtracted from that of the sample. The IC₅₀ value (the effective concentration at which the absorbance was 0.5) was calculated for each sample and standard.

RESULTS AND DISCUSSION

Characterization of isolated molecules

The structures of the compounds were established using a combination of HR-ESI-MS and NMR spectroscopy, and comparing the spectral data with literature. In exception of compound **7**, all the other compounds including myricetin 3-*O*- β -D-arabinofuranosyl (**1**),^[19] myricetin-3-*O*- β -D-glucuronic acid **2**,^[20] myricetin-3-*O*- β -D-xylofuranoside **3**,^[21] myricetin **4**, mearnsetin **5**,^[22] myricetin-3-*O*- β -D-galactopyranoside **6**,^[23] quercetin-3-(6''-galloylgalactoside) **8**, quercetin-3-*O*- β -D-glucuronic acid **9**, quercetin-3-*O*- β -D-glucopyranoside **10**,^[24] (-)-epigallocatechin-3-gallate **11**, (-)-epicatechin-3-gallate **12**,^[25] myricetin-3-*O*- α -L-rhamnopyranoside **13**, myricetin-3-*O*- β -D-glucopyranoside **14**,^[20] 3,4,5-trigalloylquinic acid **15**,^[26] (-)-epigallocatechin **16**,^[27] myricetin-3-(6''-galloylglucoside) **17** and (-)-epicatechin **18**^[25] had been reported in the literature as referenced.

Compound **7**

Compound **7** was obtained as an amorphous powder. $[\alpha]_D^{20}$ was -4.71 (c 0.857, MeOH).

The molecular formula was established as C₁₆H₂₂O₁₀S based on HR-ESI-MS and NMR data. The HR-ESI-MS in negative-ion mode showed a peak at m/z 405.0856 [M-H], (calcd. for C₁₆H₂₁O₁₀S [M-H], 405.0855) corresponding to the molecular formula C₁₆H₂₂O₁₀S. UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ϵ): 203 (1.434), 278 (0.266). IR ν^{KBr} , cm⁻¹ showed absorption bands characteristic for hydroxyl groups (3278 cm⁻¹), aromatic absorptions (1602, 1508 cm⁻¹) and a sulfonyl functional group (1456 cm⁻¹). The band at 2356 cm⁻¹ confirmed the presence of sulfur atom.

The ¹H-NMR (Table 1) showed a 1, 2, 4- trisubstituted benzene ring due to the presence of three aromatic signals typical ABX spin system. This include the double doublet at δ_H : 6.72 (J=8.3 and 1.8, H-5), which coupled to a doublet at δ_H 6.82 (d, J=1.8 Hz, H-3) and to another doublet at δ_H : 7.08 (J=8.3, H-6). The ¹H-NMR spectrum also exhibited a doublet at δ_H 4.56 (J = 7.4 Hz) characteristic of an anomeric proton of D-glucose (Table 1). It showed a singlet at δ_H

3.83 ascribed to a methoxyl group. The ^1H -NMR spectrum displayed an AMX system of allylic protons consisting of a doublet at δ_{H} 3.32 ($J = 7.3$ Hz), a multiplet at 5.99, two double doublets at 5.03 ($J = 10.0, 1.7$) and 5.05 ($J = 17.1, 1.7$). The ^{13}C NMR spectrum of **7** (Table 1) displayed 16 signals including : 6 aromatic carbons, 6 carbons attributed to the sugar moiety, three carbons of allylic group, and one methoxyl carbon. The HMBC experiment showed the linkages of the allylic moiety, the methoxyl group and the glycosyl unit to the benzene ring by the correlations of δ_{H} 3.32 (H-7) with the carbon at δ_{C} 139.9 (C-4), δ_{H} 3.83 (OCH₃) with the carbon at δ_{C} 151.9 (C-2) and δ_{H} 4.56 (H'-1) with the carbon at δ_{C} 147.8 (C-1).

The structure of compound **7** is similar to that of eugenyl *O*- β -D-glucopyranoside,^[28] except by the presence of the sulfonyl group (Table 1). This observation was confirmed by IR and the HR-ESI-MS. Compound **7** showed an additional unit of mass m/z 81, corresponding to HSO₃ group, which deshielded the carbon C-6' (66.3 ppm in the compound **7** against 63.3 ppm in eugenyl-*O*- β -D-glucopyranoside). Consequently, the preceding analysis indicates that the structure of compound **7** corresponds to the new compound, eugenyl-*O*- β -D-(6'-sulphonylglucopyranoside) (Fig. 1).

Table 1: ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectroscopic data of **7**, in CD₃OD

Compound 7			eugenyl <i>O</i> - β -D-glucopyranoside (Lit)	
	δ_{C}	δ_{H} (m, J in Hz)	δ_{C}	δ_{H} (m, J in Hz)
1	147.8	-	147.1	-
2	151.9	-	151.5	-
3	119.4	6.82 (1H, d (1.8)	119.0	6.82 (1H, d, 1.5)
4	139.9	-	139.8	-
5	123.0	6.72 (1H, dd, 8.3, 1.8)	122.9	6.72 (1H, dd, 8.2, 1.5)
6	115.0	7.08 (1H, d, 8.3)	114.9	7.08 (1H, d, 8.2)
7	41.3	3.32 (2H, d, 7.3)	41.6	3.32 (2H, d, 6.7)
8	137.5	5.99 (1H, m)	137.2	5.95 (1H, dd, t, 10.1, 6.7, 17.1)
9	117.5	5.03 (1Ha, dd, 10.0, 1.7) ; 5.05 (1Hb, dd, 17.1, 1.7)	116.7	5.03 (1Ha, dd, 9.7, 1.5)
1'	103.9	4.56 (1H, d, 7.4)	103.8	5.05 (1Hb, dd, 17.1, 1.5)
2'	75.7	3.49 (1H, dd, 9.3 ; 7.4)	75.7	4.84 (1H, d, 7.3)
3'	78.5	3.43 (1H, dd, 9.3, 8.8)	79.0	
4'	72.4	3.38 (1H, dd, 9.0; 8.8)	72.1	
5'	76.2	3.62 (1H, m)	78.6	
6'	66.3	4.29 (1Ha, dd, 11.8, 6.7) ; 4.51 (1Hb, dd (11.8, 2.3)	63.3	3.68 (1Ha, dd, 11.9, 4.7)
OMe	57.6	3.83 s	57.4	3.87 (1Hb, d, 11.9)
				3.83 s

Antioxidant activity

The antioxidant activity of 10 of the compounds were evaluated by the DPPH (2, 2'-diphenyl-1-picrylhydrazyl) scavenging, and CUPRAC method. The results obtained are reported in Table 2. All the compounds showed high activities in CUPRAC test than scorbic acid and trolox. Compound **18** displayed the highest DPPH scavenging activity with an IC_{50} $7.8 \pm 0.1 \mu\text{g} / \text{mL}$. Compounds **4**, **2**, and **13** followed with IC_{50} s $18.6 \pm 4.5 \mu\text{g} / \text{mL}$, $20.0 \pm 0.1 \mu\text{g} / \text{mL}$ and $20.0 \pm 0.9 \mu\text{g} / \text{mL}$ respectively. These results corroborate with those of the literature. Indeed, epicatechin (**18**) is known for its powerful antioxidant activity.^[29, 30] Likewise, authors have indicated that hydroxy groups in the ortho position on the B ring of flavonoids could increase the antioxidant effect of a compound, while sugar substituents in position 3 of the C ring reduces the antioxidant activity.^[31] The Antioxidant activity of epicatechin (IC_{50} $7.8 \pm 0.1 \mu\text{g} / \text{mL}$), myricetin (IC_{50} $18.6 \pm 4.5 \mu\text{g} / \text{mL}$), myricetin-3-*O*- β -D-glucuronic acid (IC_{50} $20.0 \pm 0.1 \mu\text{g} / \text{mL}$) and myricetin-3-*O*- α -L-rhamnopyranoside (IC_{50} $20.0 \pm 0.9 \mu\text{g} / \text{mL}$) are respectively more active than the controls, ascorbic acid (IC_{50} 23.17 ± 2.02) and quercetin (IC_{50} $31.67 \pm 2.88 \mu\text{g} / \text{mL}$).

Table 2. DPPH radical scavenging and CUPRAC radical scavenging activities of isolated compounds from *L. welwitschii* and *L. acida*

	Products tested	Test de DPPH	Test de CUPRAC
Positive controls	Ascorbic acid	23.17 ± 2.02	93.33 ± 5.77
	Quercetin	31.67 ± 2.88	18.67 ± 1.15
	Trolox	-	81.67 ± 12.58
<i>L. welwitschii</i>	4	$18.6 \pm 4,5$	160 ± 8
	5	49 ± 15	233 ± 17
	2	20.0 ± 0.1	85 ± 5
<i>L. acida</i>	17	$77.0 \pm 1,5$	37 ± 7
	13	20.0 ± 0.9	54.0 ± 1.4
	14	40.0 ± 0.1	231.0 ± 4.7
	10	-	27.6 ± 6.2
	18	$7.8 \pm 0,1$	52.3 ± 2.1
	11	42.0 ± 0.7	53.3 ± 7.7
	12	-	25.0 ± 7.3

CONCLUSION

Together, *Lannea acida* and *Lannea welwitschii* yielded eighteen compounds including the new eugenyl-*O*- β -D-(6'-sulphonylglucopyranoside) from *Lannea acida*. As far as we know, these compounds were reported for the first time in these plants. Four of the compounds including **4**, **2**, **13** and **18** have potent antioxidant activity. The antioxidant activities of these compounds could explain the usefulness of these herbs in traditional medicine against several diseases.

Further studies of anti-inflammatory and anticancer activities of isolated compounds should be considered to validate the claims for their use, especially in the management of cancer.

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