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α-Glucosidase inhibitory constituents from stem bark of *Terminalia superba* (Combretaceae)

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Abstract

The CH_2Cl_2/CH_3OH (1/1) extract of the dried stem bark of *Terminalia superba* afforded two compounds, (7*S*,8*R*,7′*R*,8′*S*)-4′-hydroxy-4-methoxy-7,7′-epoxylignan and *meso*-(*rel* 7*S*,8*R*,7′*R*,8′*S*)-4,4′-dimethoxy-7,7′-epoxylignan along with 11 known compounds. The structures of the compounds were established by analysing the spectroscopic data and also comparing it with the data of previously known analogues. All the isolated compounds were evaluated for their glycosidase inhibition activities. Gallic acid and methyl gallate showed significant α-glucosidase inhibition activity.

Keywords: *Terminalia superba*; Combretaceae; Stem bark; Lignans; Gallic acid; α-Glucosidase activity

1. Introduction

Terminalia superba Engl. and Diels (Combretaceae) is a plant used by traditional healers as a remedy for diabetes mellitus in Africa. The Sotho people of Southern Senegal take the powdered stem bark of this plant against diabetes. In Niger and in Mali this plant is used to treat hepatitis (Ajanohoun et al., 1979, 1980). *Terminalia superba* is a big tree, up to 50 m in height and 120 cm in stem diameter, with deciduous leaves. It is widely distributed in the dense humid forests, semi-deciduous forests and also in easily flooded and secondary forests (Burkill, 1985). Both the methanol and methylene chloride extracts of the stem bark of *Terminalia superba* were previously reported to have anti-diabetic activity (Kamtchouing et al., 2006). The methanol extract of *Terminalia superba* also induces endothelium-independent relaxation of rat thoracic aorta (Dimo et al., 2006). The widespread use of *Terminalia superba* in indigenous medicine for different ailments, as well as the significant anti-diabetic activity and vasorelaxant effects exhibited by extracts obtained from *Terminalia superba*, justified further attempts to isolate and identify active compounds. In this paper, we report the isolation and the structural elucidation of two new lignans, and the α-glucosidase inhibition study of some isolated compounds.

2. Results and discussion

The stem bark of *T. superba* was extracted with a mixture of CH_2Cl_2/MeOH (1/1). The extract which showed

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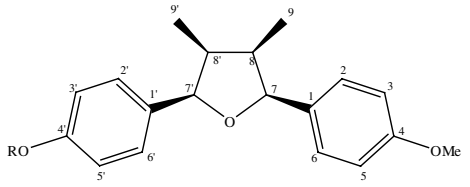
considerable α-glucosidase inhibitory activity, was separated using repeated column chromatography and preparative TLC (PTLC) to afford two new compounds and eleven known compounds identified as ellagic acid, ellagic acid 3,3′-dimethyl ether, ellagic acid-4-*O*-β-D-xylopyranoside-3,3′-dimethyl ether, gallic acid, methyl gallate, oleanolic acid, betulinic acid, lupeol, β-amyrin, stigmasterol and β-sitosterol respectively, by comparison of their spectroscopic data with those of authentic samples or values reported in the literature (Atta-ur-Rahman et al., 2002; Khac et al., 1990; Tanaka et al., 1998).



1 R = H

2 R = Me

Compound **1**, $[\alpha]_D^{25} = +35.0°$, was obtained as a white powder. Its molecular formula $C_{19}H_{22}O_3$ was deduced from the CIMS, EIMS and HR EIMS ($[M]^+$, *m/z* found 298.1527, calc. 298.1560). The UV spectrum showed two maxima at 277 and 227 nm, suggesting the presence of a tetrahydrofuran lignan (Urzua et al., 1987). The ^1H NMR spectrum (Table 1), showed characteristic signals arising from the tetrasubstituted tetrahydrofuran ring system comprising of two secondary methyl groups at δ 0.55 and 0.57 (*d*, *J* = 5.7 Hz), a two-proton multiplet at δ 2.68 (*ddq*, *J* = 5.8; 5.7; 3.1 Hz) due to the H-8 and H-8′ methine protons, and a two proton doublet at δ 5.10 (*d*, *J* = 5.8 Hz) due to the two oxymethine protons, H-7 and H-7′. The ^1H NMR spectrum of **1**, showed one additional methoxyl at δ 3.80 (*s*) and two AA′BB′ systems for aromatic protons at δ 6.81 (*d*, *J* = 8.5 Hz, H-3 and H-5), 6.88 (*d*, *J* = 8.8 Hz, H-3′ and H-5′), 7.27 (*d*, *J* = 8.4 Hz, H-2 and H-6) and 7.31 (*d*, *J* = 8.6 Hz, H-2′ and H-6′) implying that each aromatic ring has a 1,4-disubstitution pattern. The presence of tetrahydrofuran lignan was confirmed by the observation of two methyl groups, twelve methine groups and four quaternary carbon resonances in the ^{13}CNMR spectrum (Table 1). Complete assignment of the proton spin systems in **1** was achieved by COSY ^1H–^1H and 2D-NOESY, while carbons were assigned from HMQC and HMBC spectra. The analysis of the HMBC spectrum permitted the attribution of aromatic hydroxyl and the *O*-methyl signals. The relative configuration at C-7, C-7′, C-8 and C-8′ was assigned by a combination of NOE data and analysis of the chemical shifts H-7/H-7′, the methyl protons (Me-9/Me-9′) and C-7/C-7′ (Rimando et al., 1994). Me-9 showed a NOE correlation with the Me-9′ proton resonance and with the *ortho* proton of the phenolic ring, Me-9′ showed NOEs with Me-9, and the *ortho*-proton of the methoxy-bearing aromatic ring. This finding clearly establish the *cis*-relation of the two methyl groups, as well as the *cis*-relation between the two methyl groups and their vicinal aryl substituents. This was confirmed by the chemical shift of the methyl groups (δ 0.55, Me-9; δ 0.57, Me-9′), which are clearly shielded by the neighbouring aromatic rings, and gave evidence for the *cis*-relation, compared with those of (7*S*,8*S*,7′*S*,8′*S*)-3,3′,4′-trihydroxy-4-methoxy-7,7′-epoxylignan (Abou-Gazar et al., 2004), and *rel*- (7*S*,8*S*,7′*R*,8′*R*)-3,3′,4,4′,5,5′-hexamethoxy-7.0.7′,8, 8′-lignan (Conserva et al., 1990). The coupling constants between the H-7 and H-8 and H-7′ and H-8′ (*J* = 5.8 Hz) indicated a 7,8-*cis*-7′,8′-*cis* relationship. All these informations are in agreement with the proposed structure **1** (or enantiomer). The absolute configuration of **1** was assigned by a combination of analysis of the CD spectrum and comparison of optical rotation data ($[\alpha]_D^{25} = +35.0°$ (*c* = 0.007 in MeOH)) data with those of 7,7′-epoxylignans (Urzua et al., 1987; Minh Giang et al., 2006; Prasad et al., 1998). The CD spectrum showed negative cotton effects in both the 240–250 and

Table 1
^1H (500 MHz) and ^{13}C (125 MHz) assignments for **1** and **2** in $CDCl_3$

Attribution	**1**		**2**	
	^{13}C	^1H	^{13}C	^1H
1	132.6	–	133.0	–
2/6	127.5	7.27 (*d*, *J* = 8.4)	128.0	7.30 (*d*, *J* = 8.6)
3/5	113.4	6.81 (*d*, *J* = 8.5)	112.4	6.74 (*d*, *J* = 8.6)
4	154.3	–	155.3	–
7/7′	82.6	5.10 (*d*, *J* = 5.8)	83.5	5.12 (*d*, *J* = 6.1)
8/8′	41.5	2.68 (*ddq*, *J* = 5.8; 5.7; 3.1)	42.9	2.62 (*m*)
1′	132.9	–	133.0	–
2′/6′	127.7	7.31 (*d*, *J* = 8.6)	128.2	7.30 (*d*, *J* = 8.6)
3′/5′	114.8	6.88 (*d*, *J* = 8.6)	115.3	6.74 (*d*, *J* = 8.6)
4′	158.5	–	159.5	–
OH	–	4.69 (*s*)	–	4.75 (*s*)
Me-9	11.8	0.55 (*d*, *J* = 5.7)	12.0	0.57 (*d*, *J* = 5.8)
Me-9′	11.8	0.57 (*d*, *J* = 5.7)	12.0	0.57 (*d*, *J* = 5.8)
MeO	55.2	3.80 (*s*)	56.0	3.83 (*s*)

Assignments were based on HMQC, HMBC and NOESY experiments.

280–300 nm regions ^{1}La and ^{1}Lb for the aromatic transitions suggesting that **1** possesses the 7*S*, 8*R*, 7′*R*, and 8′*S* absolute configuration. The structure of **1** may be defined as (7*S*, 8*R*, 7′*R*, 8′*S*)-4′-hydroxy-4-methoxy-7, 7′-epoxylignan. The isomer of this compound was identified from the petrol chloroform extracts of *Krameria triandra* roots (Facino et al., 1997).

Compound **2** displayed a molecular ion at *m*/*z* 312 (HREIMS *m*/*z* 312.1725 calc. 312.1739), 14 mass units higher than that of **1**, suggesting a molecular formula $C_{20}H_{24}O_3$, and hence replacement of the hydroxyl moiety by a methoxyl group. Inspection of the ^{1}H and ^{13}C NMR spectra of **2** indicated typical spin patterns of a C-10 dimer, which contained only 12 protons [aromatic protons: 2 × AA′BB′ systems; δ 6.74 (*d*, $J = 8.6$ Hz, H-3, H-5, H-3′ and H-5′), 7.30 (*d*, $J = 8.6$ Hz, H-2, H-6, H-2′ and H-6′), tetrahydrofuranoid protons δ 2.62 (*m*, H-8 and H-8′), 5.12 (*d*, $J = 6.1$ Hz, H-7 and H-7′), two methoxyl, and two methyl groups], and ten carbons. The symmetry shown by the ^{1}H and ^{13}C NMR spectra data was supported by the optical rotation value $[\alpha]_D^{25} = 0°$ ($c = 0.010$ in $CHCl_3$), indicating that **2** was a *meso* diastereoisomer. There are two *meso* forms of 3,4,3′,4′-tetrahydroxy-7,7′-epoxylignan, which differ in orientation of the two methyl groups and which can be distinguished on the basis of their chemical shifts as shown above (Rimando et al., 1994). The methyl and the oxymethine protons of **2** displayed signals at δ 0.57 and 5.12, respectively, while the resonances of C-7/C-7′ and C-8/C-8′ were at δ 83.5 and 42.9, respectively, which verified that **2** is the 7,8-*cis*-7′,8′-*cis meso* form. Compound **2** is thus *meso*-(*rel* 7*S*, 8*R*, 7′*R*, 8′*S*)-4, 4′-dimethoxy-7, 7′-epoxylignan.

When tested again three common glycosidases, gallic acid and methyl gallate showed the highest selective glucosidase inhibition. The gallic acid showed inhibition, which is twice more active than the methyl gallate, perhaps the acid function is more important for activity than the ester group. Ellagic acid, ellagic acid 3,3′-dimethyl ether, ellagic acid-4-*O*-β-D-xylopyranoside-3,3′-dimethyl ether are less active (118.7 ± 0.03 μM; 184.6 ± 0.9 μM; 194.1 ± 0.2 μM) than the gallic acid derivatives despite the presence of phenolic hydroxyl groups. The gallic acid derivatives showed significantly higher inhibition of yeast alpha-glucosidase than deoxynojirimycin (425.6 ± 8.1 μM), which is one of the most potent α-glucosidase enzyme inhibitors. The inhibition of α-glucosidase would limit the absorption of dietary carbohydrates and in turn suppress postprandial hyperglycemia. Gallic acid and ellagic acid derivatives may be the main anti-hyperglycemic agents present in this plant, as it has been shown to induce an anti-diabetic effect.

3. Experimental

3.1. General

The melting points were recorded on a Buchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-360 digital polarimeter using a 10 cm cell in methanol. Ultraviolet spectra were recorded on a Hitachi UV 3200 spectrophotometer in MeOH. Infrared spectra were recorded on a JASCO 302-A spectrophotometer. The mass spectra were recorded on a Varian MAT 311A mass spectrometer. Accurate mass measurements were carried out with a FAB source using glycerol as matrix, and HREIMS were taken on a JEOL HX 110 mass spectrometer. The ^{1}H and ^{3}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, on Bruker AMX 500 NMR spectrometers. Methyl, methylene and methine carbons were distinguished by DEPT experiments. Homonuclear 1H connectivities were determined by using the COSY experiment. One bond ^{1}H–^{13}C connectivities were determined with HMQC gradient pulse factor selection. Two- and three-bond ^{1}H–^{13}C connectivities were determined by HMBC experiment. Chemical shifts were reported in δ (ppm) using TMS as internal standard and coupling constants (*J*) were measured in Hz. Column chromatography was carried out on silica gel (70–230 mesh, Merck) and flash silica gel (230–400 mesh, Merck). TLC was performed on Merck precoated silica gel 60 F_{254} aluminum foil, and spots were detected using ceric sulfate spray reagent. All reagents used were of analytical grades.

3.2. Plant material

The stem bark of *T. superba* was collected in July 2004 near Bertoua, East Cameroon. The herbarium specimen documenting the collection has been deposited in the National Herbarium, Yaounde, Cameroon (Ref. No. 6516 SRF/CAM).

3.3. Extraction and isolation

Powdered, air-dried stem bark of *T. superba* (4.5 kg) was extracted with CH_2Cl_2/MeOH (1/1) at room temperature for 72 h. After removing the solvents by evaporation under reduced pressure, the resultant crude extract (200.5 g) was chromatographed over silica gel 60 (230–400 mesh), using hexane, CH_2Cl_2 and MeOH in increasing polarity order. A total of 150 sub-fractions (ca. 250 ml each) were collected and combined on the basis of TLC analysis leading to six main fractions A–F.

Fraction A was chromatographed over silica gel 60C (20–40 μm) column with a hexane–CH_2Cl_2 gradient. A total of 35 fractions of ca. 100 ml each were collected and combined on the basis of TLC. Fractions 1–30 were further chromatographed over silica gel 60 H (5–40 μm), with a mixture of hexane–CH_2Cl_2 (9:1) to yield (7*S*,8*R*,7′*R*,8′*S*)-4′-hydroxy-4-methoxy-7,7′-epoxylignan (**1**) (16.0 mg) and *meso*-(*rel* 7*S*,8*R*,7′*R*,8′*S*)- 4,4′-dimethoxy-7,7′-epoxylignan (**2**) (18.0 mg), lupeol (15 mg), *β*-amyrin (6.2 mg). Main fraction B was chromatographed over silica gel 60C (20–40 μm) column with a hexane–CH_2Cl_2 gradient. A total of 25 fractions of ca. 100 ml each were collected and combined on the basis of TLC. Fractions 1–10 were further

Table 2
Glycosidase inhibition of some isolated compounds

Compound	α-D-Glucosidase (yeast) $IC_{50} \pm$ sem	β-D-Glucosidase (sweet almonds) $IC_{50} \pm$ sem	α-D-Mannosidase (jack bean) $IC_{50} \pm$ sem
Gallic acid	5.2 ± 0.2	15.6 ± 0.5	194.4 ± 0.2
Methyl gallate	11.5 ± 0.1	45.3 ± 0.2	NI
Ellagic acid	194.1 ± 0.2	260.0 ± 0.7	NI
Ellagic acid 3,3′-dimethyl ether	184.6 ± 0.9	NI	NI
Ellagic acid-4-*o*-β-D-xylopyranoside-3,3′-dimethyl ether	118.7 ± 0.1	NI	NI
1	NI	NI	NI
2	NI	NI	NI

NI no inhibition at 800 μM concentration.

chromatographed over silica gel 60H (5–40 μm) with a mixture of hexane–CH_2Cl_2 (4:1) to yield stigmasterol (24.0 mg) and β-sitosterol (10.0 mg). Main fraction C was chromatographed over silica gel 60C (20–40 μm) column with a hexane–CH_2Cl_2 gradient. A total of 25 fractions of ca. 100 ml each were collected and combined on the basis of TLC. Fractions 21–30 were further chromatographed over silica gel 60H (5–40 μm) with a mixture of hexane–CH_2Cl_2 (7:3) to yield betulinic acid (15.0 mg) and oleanolic acid (10.0 mg). Main fraction E was chromatographed over silica gel 60C (20–40 μm) column with a CH_2Cl_2–MeOH gradient. A total of 25 fractions of ca. 100 ml each were collected and combined on the basis of TLC. Fractions 1–10 were further chromatographed over silica gel 60H (5–40 μm) with pure CH_2Cl_2 to yield methyl gallate (32.0 mg). Fractions 11–35 were further chromatographed over silica gel 60H (5–40 μm) with a mixture of CH_2Cl_2–MeOH to yield gallic acid (20.0 mg), ellagic acid (25.0 mg), ellagic acid 3,3′-dimethyl ether (55.0 mg), ellagic acid-4-*O*-β-D-xylopyranoside-3,3′-dimethyl ether (50.0 mg).

3.3.1. (7*S*,8*R*,7′*R*,8′*S*)-4′-hydroxy-4-methoxy-7,7′-epoxylignan (**1**)

white powder; mp 110–113 °C; $[\alpha]_D^{25} = +35.0°$ ($c = 0.007$ in MeOH); CD $\{\theta\}_{240}$–5.20; $\{\theta\}_{250}$ −8.45; $\{\theta\}_{280}$–4.68; $\{\theta\}_{290}$–9.56; UV λ_{max}^{MeOH} (log ε) nm: 277 (3.87), 250 (2.50), 240 (2.64), 227 (3.60); IR (KBr) υ_{max} 3340, 2930, 1615, 1455, 1230, 1040 cm^{-1}; ^1H NMR and ^{13}C NMR see Table 1; HR EIMS *m*/*z* 298.1527 (calc. for $C_{19}H_{22}O_3$298.1560); EIMS *m*/*z* (rel. int.): 298 (14) $[M]^+$, 162 (100), 147 (77), 136 (17), 135 (18), 107 (15).

3.3.2. meso-(rel 7*S*,8*R*,7′*R*,8′*S*)-4,4′-dimethoxy-7,7′-epoxylignan (**2**)

white powder; mp 98–100 °C; $[\alpha]_D^{25} = 0°$ ($c = 0.010$ in $CHCl_3$); UV λ_{max}^{MeOH} (log ε) nm: 275 (3.87), 250 (2.50), 240 (2.64), 200 (3.60); IR (KBr) υ_{max}:, 2931, 2877, 1697, 1649, 1517, 1460, 1392, 1222, 1053 cm^{-1}; ^1H NMR and ^{13}C NMR see Table 1; HR EIMS *m*/*z* 312.1725 (calc. for $C_{20}H_{24}O_3$312.1739); EIMS *m*/*z* (rel. int.): 312 (13) $[M]^+$, 297 (16), 282 (53), 176 (58), 162 (100), 147 (25), 136 (18), 121 (24).

3.4. α-Glucosidase activity

The glycosidase inhibition assay was performed according to the slightly modified method of Oki et al. (Oki et al., 1999). Activity of the compounds has been determined against α-D-glucosidase (E.C. 3. 2. 1. 20), β-D-glucosidase (E.C. 3. 2. 1. 21), and α-D-mannosidase (E.C. 3. 2. 1. 24), purchased from Wako Pure Chemical Industries Ltd. Osaka, Japan (Wako 076-02841). The inhibition was measured spectrophotometrically at 37 °C using 1 mM *p*-nitrophenyl α-D-glucopyranoside, and *p*-nitrophenyl β-D-glucopyranoside as a substrate at pH 6.9, then at pH 4.0 using 1 mM *p*-nitrophenyl α-D-mannopyranoside and 500 units/ml enzymes, in 50 mM sodium phosphate buffer containing 100 mM NaCl. 1-deoxynojirimycin (0.425 mM) was used as positive control. The increment in absorption at 400 nm due to the hydrolysis of PNP-G by glycosidase was monitored continuously with a Molecular Devices USA spectrophotometer Table 2.

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