ORIGINAL ARTICLE

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Rec. Nat. Prod. 8:4 (2014) 323-329

records of natural products

New Secondary Metabolites from *Quercus coccifera* L.

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(Received June 5, 2013; Revised October 21, 2013; Accepted January 10, 2014)

Abstract: Three new secondary metabolites kermesoside (**1**), cocciferoside (**2**) and (-)-8-chlorocatechin (**3**), were isolated from the the stems with barks of *Quercus coccifera* along with five known phenolic compounds, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one (**4**) and 3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-propan-1-one (**5**), trans-resveratrol-3-O-*β*-glucopyranoside (**6**) lyoniresinol-9-O-*β*-xylopyranoside (**7**), lyoniresinol-9-O-*β*-glucopyranoside (**8**). The structure elucidation of the isolated compounds was performed by spectroscopic methods (UV, 1D- and 2D- NMR and HR-MS).

Keywords: *Quercus coccifera*; megastigmane glycoside; phenolic compounds; spectroscopic analysis.

1. Introduction

Genus *Quercus* L. (Fagaceae), is comprising over 200 species in temperate areas of Northern hemisphere and tropical mountains [1]. Plants of the genus *Quercus* have been used as traditional medicinal plants in various parts of the world as antiseptic, hemostatic, for the treatment of diarrhea, hemorrhoid [2-3] and some of them possess antimicrobial, antiinflammatory, gastroprotective, antioxidant, cytotoxic, antitumoural properties [4-6]. Furthermore, the decoction of these plants can be used for burns and added to ointments for the healing of cuts [3]. Bark decoction of *Q. coccifera* L. is used for the treatment of diabetes and diarrhea [7] and called as “kermes oak” in Anatolia [1]. The genus *Quercus* is known to contain various classes of compounds such as saponins, flavonoids and especially tannins [4-5, 8]. Due to the use of *Quercus* species in the construction of wine barrels and the interactions between wine and oak wood during the maturation of wine, these plants have been the subject of intensive research. Some hydrolysable tannins from the leaves of *Q. coccifera* were isolated previously [9], but there is no phytochemical report on stems and barks of this plant. As a part of our ongoing researches on *Quercus* species [4-6], we have investigated *Q. coccifera*. In this paper we report the isolation and structure elucidation of three new secondary metabolites 2,6-bis(hydroxymethyl)-4-methoxyphenyl-*β*-glucopyranoside (kermesoside) (**1**), 5,6-dihydro- *β* -ionone 3-O-*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside (cocciferoside) (**2**) and ((-)-8-chlorocatechin (**3**) from *Q. coccifera*, together with five known metabolites, two simple phenol; (3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one (**4**) and 3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-

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The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/RNP © Published 07/05/2014 EISSN:1307-6167

propan-1-one (**5**), a stilbene derivative; (*trans*-resveratrol-3-O-*β*-glucopyranoside (**6**)) and two lignans (lyoniresinol-9-O-*β*-xylopyranoside (**7**) and lyoniresinol-9-O-*β*-glucopyranoside (**8**)).

2. Materials and Methods

2.1. General

TLC: precoated *Silica gel 60 F_{254} (Merck)* aluminium plates, elution with $CHCl_3$/MeOH/H_2O mixtures; visualization by spraying 10% H_2SO_4, followed by heating at 105 ºC for 1-2 min. Column chromatography (CC): Silica gel *60* (0.063-0.200 mm; *Merck*) and Sephadex LH-20 (*Sigma*), polyamide (*Fluka*). Vacuum liquid chromatography (VLC): reversed-phase *Lichroprep RP-18* (25–40 mm; *Merck*). Middle pressure liquid chromatography (MPLC): reversed-phase *Lichroprep RP-18* (25–40 mm; *Merck*), *Büchi* 681 chromatography pomp. Optical rotations: *Rudolph Autopol-IV Automatic* polarimeter, in MeOH. UV Spectra: *Bio-Tek Instruments*, *M-Quant Biomolecular* spectrophotometer; λ_{max} in nm. NMR spectra were recorded in methanol-d_4 at room temperature with a *Bruker Avance DRX-500* spectrometer. Chemical shifts were given on the δ-scale and were referenced to the solvent (δ_C = 49.15, δ_H = 3.31). The pulse programs of all experiments (^{1}H, ^{13}C APT, gs-HMQC, gs-HMBC, gs-COSY, ROESY, HMQC-TOCSY) were taken from the Bruker Software library. HRMS: *LTQ FT Ultra*, (*Thermo Finnigan*, San Jose, CA) system. The ionization method was ESI and operated in positive ion mode, in *m/z*.

2.2. Plant Material

Q. coccifera L. (Fagaceae) was collected from Sertavul- Akçeşme between Mut and Konya (Middle-South Anatolia, Turkey), near roadway, 1600 m in August 2008. A voucher specimen has been deposited in the Herbarium of the Faculty of Pharmacy, Hacettepe University, Ankara, Turkey (HUEF 10003).

2.3. Extraction and Isolation

The air-dried, powdered the stems with barks of *Q. coccifera* (297 g) were extracted with MeOH (4 × 2 L) at 45 ˚C. The combined MeOH extracts were dried in vacuo and lyophilized (21.5 g, 7.2%). The MeOH extract (10 g) was subjected to polyamide (150 g) column chromatography (CC) (H_2O/MeOH: 100/0, 50/50, 0/100 %) to afford 8 fractions (Fr. A–H). Fr. B was rechromatographed over *silica gel* CC eluting with stepwise $CHCl_3$–MeOH gradient (0–60% MeOH) to obtain subfractions $B_{1–5}$. Fr. B_2 was further purified by C18-VLC (H_2O:MeOH) to yield 4 mg **1** (H_2O-MeOH, 9:1). Fr. B_4 was also subject to C18-VLC and 3.8 mg **2** was isolated. Fr. C was applied to *silica gel* CC eluting with stepwise $CHCl_3$–MeOH gradient (0–100% MeOH) to yield fractions Frs. C_{1-7}. Fr. C_2 was further purified by C18-VLC and 2.5 mg mixture of **4** and **5** (H_2O–MeOH, 92.5:7.5) was obtained. Fr. C_4 was applied to VLC to give **7** with (H_2O–MeOH, 7:3) (10 mg). Fr. C_6 was also subject to VLC system and with H_2O–MeOH (7:3), compound **8** (5 mg) was isolated. Fr. E was subjected to *silica gel* CC eluting with stepwise $CHCl_3$–MeOH gradient (0–50% MeOH) to afford Frs. E_{1-3}. Fr E_2 was applied to MPLC system to give 10 mg **6** H_2O–MeOH (67.5:32.5). Fr. F was subjected to a silica gel CC and eluted with increasing polarity of $CHCl_3$-MeOH- H_2O solvent system and Frs. F_{1-3} were obtained. Fr. F_2 was applied to VLC and 8.8 mg **3** was isolated.

1) *kermesoside,(2-(2,6-bis(hydroxymethyl)-4-methoxyphenoxy)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol)*; $[\alpha]^{25}_D$ = -7.1 (c=0.1, MeOH). ^{1}H- and ^{13}C-NMR: see Table 1. HR-MS: 369.11530 ([*M*+Na]$^-$, $C_{15}H_{22}O_9Na$; calc. 369.11560).

2) *cocciferoside, 3-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside5,6-dihydro-β-ionone, ((E)-4-((1R,4S,6R)-4-((2R,3R,4S,5S,6R)-6-(((2R,3R,4R)-3,4-dihydroxy-4-(hydroxymethyl)-tetrahydrofuran-2-yloxy)methyl)-3,4,5-trihydroxy-tetrahydro-2H-pyran-2-yloxy)-2,2,6-trimethylcyclohexyl)but-3-en-2-one)*; $[\alpha]^{25}_D$ = -35.5 (c=0.1, MeOH). UV (MeOH): 204 (3.86). ^{1}H- and ^{13}C-NMR: see Table 2. HR-MS: 527.24632 ([*M*+Na]$^-$, $C_{24}H_{40}O_{11}Na$; calc. 527.24628).

3) *(-)-8-chlorocatechin (8-chloro-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol)*; $[\alpha]^{25}_{D}$ = -30.19 (c=0.1, MeOH). UV (MeOH): 213 (4.21), 303 (4.29). ^{1}H- and ^{13}C-NMR: see Table 3. HR-MS: 323.03221 ([M-H]$^{-}$, $C_{15}H_{12}O_6Cl$; calc. 323.03279).

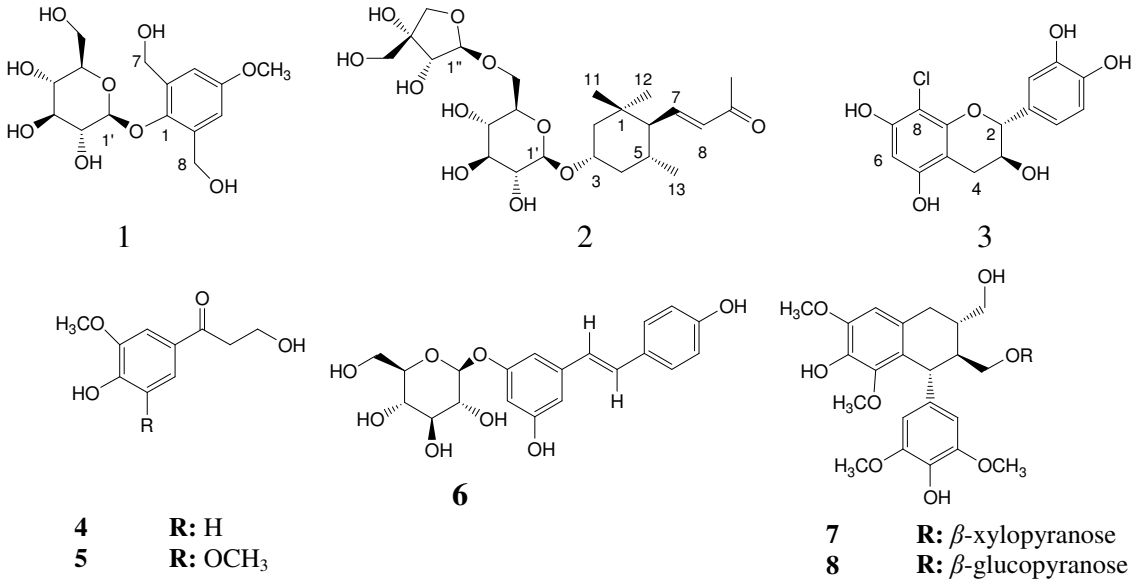

Figure 1. The structures of compounds 1-8

3. Results and Discussion

The stems with barks of *Q. coccifera* extracted with MeOH. The crude MeOH extract was firstly fractioned by *polyamide* column chromatography and compounds **1-8** were obtained by further column chromatographic separations.

3.1. Structure elucidation

Compound **1** was isolated as amorphous powder. Its molecular formula was determined as $C_{15}H_{22}O_9$ by positive-ion ESI-HR-MS ([*M*+Na]$^{+}$ at 369.11530). The ^{1}H-NMR spectrum of **1** showed a singlet signal at δ_H 6.71 (2H) for the magnetically equivalent H-3 and H-5, expressed the presence of 1,2,4,6 tetrasubstituted phenyl group. The anomeric proton resonance at δ_H 4.84 (*d, J*=7.5 Hz) and the signals in the region δ_H 3.77-3.20 together with the corresponding ^{13}C-resonances indicated the presence of *β*-glucopyranosyl (Glc) unit [10]. Furthermore, signals for a methoxy group at δ_H 3.85 (3H) and two methylene at δ_H 4.55 observed in the ^{1}H-NMR spectrum of **1**. The ^{13}C NMR spectrum of **1** exhibited 12 C signals, 4 of them were attributed to phenyl ring, 6 of them were attributed to *β*-glucopyranosyl ring, one of them were attributed to methylene carbons (C(7) and C(8)) at phenyl ring and one of them were attributed to methoxy carbon atom. HMBC between H-1' and C(1) assigned the position of the *β*-glucopyranosyl unit at C(1) of the phenyl ring, while the HMBC cross peak between methoxy protons and C(4) and the ROESY correlations H-7,8/H-1', H-7,8/H-3,5 and H-3,5/hydrogens of methoxy group allowed us to determined structure of **1** as (2,6-bis(hydroxymethyl)-4-methoxyphenyl-*β*-glucopyranoside and named kermesoside.

Compound **2** obtained as an amorphous powder. Two olefinic protons observed at δ_H 6.66 (*dd, J*=5.5, 15.8 Hz) [H-7] and 6.08 (*d, J*=15.8 Hz) [H-8] were consistent with an *E*-disubstituted double bond. COSY correlations were observed from H-7 to H-8 and to a methine proton at δ_H 1.58 (*t, J*=10.5 Hz) [H-6]. Four methyl groups were observed as three methyl singlets Me-10 δ_H 2.26, Me-11 δ_H 0.95, Me-12 (δ_H 0.89, and a methyl doublet Me-13 δ_H 0.84 (*d, J*=6.5 Hz) with a COSY correlation to a methine at δ_H 1.76 (*m*) [H-C(5)]. The HMBC correlations of methyl groups, the H-2 δ_H 1.88/H-3 and

H-4 δ_H 2.19/H-C(3) established the presence of the aglycone moiety 3-hydroxy-5,6-dihydro-β-ionone [11, 12] (**2**, Figure 1). Two resonances observed in the anomeric spectral region indicate the presence of two glycosidic units. Identification and assignment of the ^{1}H and ^{13}C resonances belonging to these units was based on signal correlations observed in 1D-TOCSY and HMBC spectra. The coupling pattern of the glycosidic protons as well as chemical shifts of corresponding carbon resonances unequivocally pointed out, that the two glycoside units in compound **2** were composed of a glucopyranose and an apiofuranose moieties. Based on the value of the coupling of the anomeric protons [δ_H 4.35 (*d, J*=7.5 Hz)] and [δ_H 5.02 (*d, J*=2.5 Hz)]), the anomeric configurations were assigned as β for the both sugar [10]. ^{13}C-NMR indicated that β-apiofuranose was in the terminal position (δ_C 111.1, 80.7, 78.2, 75.2, 65.8). A significant downfield shift δ(C6′) 68.8 (instead of 62.9) [11] observed at the 6 position of β-glucopyranose indicated that the β-apiofuranose was linked to that position. This assumption was further supported by the HMBC between the anomeric H-1" and C(6') of glucopyranose. Furthermore, the cross peaks observed between the anomeric H-1' and C(3) of aglycone in the HMBC spectrum, allowed us to assign the position of the sugar moiety at C(3). The relative configuration of the compound was determined based on the H-7/H-11, H-7/H-5, H-3/H-11, H-3/H-5, H-6/H-2 δ_H 1.22 and H-6/H-4 δ_H 1.05 NOESY correlations. The absolute configuration of the compound assigned as 3S, 5R, 6R by comparing the ^{13}C NMR data with alonginoside L (3-O-β-glucopyranosyl-5,6-dihydro-β-ionone) which is different from **2** by absence of apiofuranose [11].

Table 1. ^{1}H- and ^{13}C-NMR data[a)] and HMBC correlations for **1** (in CD_3OD; in ppm, *J* in Hz)

	δ (H)[b)]	δ (C)[c)]	HMBC (H→C)
Aglycone			
C(1)	-	135.5	
C(2, 6)	-	139.6	
H-C(3, 5)	6.71 *s*	105.8	C(1), C(2), C(4), C(6), C(7), C(8)
C(4)	-	154.5	
CH_2(7, 8)	4.55 *s*	65.3	C(2), C(6)
MeO	3.85 *s*	57.1	C(4)
Glucose			
H-C(1')	4.84 (*d, J*= 7.5)	105.6	C(1),
H-C(2')	3.48 (*dd, J*= 2.2, 7.5)	75.9	C(1"), C(3")
H-C(3')	3.42 *	78.0	C(2"), C(4"),
H-C(4')	3.42 *	71.5	
H-C(5')	3.20 (*ddd*, *J*= 2.3, 5.0, 9.3)	78.5	
CH_2(6')	3.67 (*dd, J*= 5.0, 12.0)	62.7	
	3.77 (*dd, J*= 2.3, 12.0)		

[a]All δ (H) and δ_C assignments are based on 2D NMR (DQF-COSY, HMQC, HMBC).
[b]Recorded at 500 MHz. [c]) Recorded at 125 MHz,
*Overlapping signals. Arbitrary atom numbering.

Therefore, **2** identified as a new megastigmane glycoside, 5,6-dihydro-β-ionone 3-O-β-apiofuranosyl-(1→6)-β-glucopyranoside and named cocciferoside.

Compound **3** was obtained as an amorphous powder. The HR-MS of **3** exhibited a pseudomolecular ion at *m/z* 323.03221, indicating a molecular formula of $C_{15}H_{12}O_6Cl$. Chlorine content of the sample was proved by the characteristic isotopic ratio ([M-H+2]/[M-H]=0.32) as well as the accuracy of the measured monoisotopic exact mass of the deprotonated molecular ion peak (delta=1.9 ppm). The number of rings and double bonds of the molecule was indicated by the RDB value (=9.5). The ^{13}C NMR (Table 3) spectra of **3** displayed 15 resonances. The ^{1}H-NMR spectrum of **3** showed a double doublets at δ_H 6.58 (*dd, J*=1.7, 8.0 Hz) and two doublets at δ_H 6.71 (*d, J*=1.7 Hz) and 6.69 (*d, J*=8.0 Hz) revealed the 3',4'-dihydroxy functional structure of a flavan B ring. The ^{1}H-NMR spectrum also displayed a singlet signal at δ_H 6.15 in the aromatic region, suggesting the presence of an trisubstitued A ring. The signals belonging to C ring were observed as H-2 (δ_H 4.69 (*d, J*=6.5 Hz), H-3 (δ_H 3.89 (m), H-4a (δ_H 2.41 (*dd, J*=16.2, 7.3 Hz), and H-4b (δ_H 2.59 (*dd, J*=16.2, 5.2 Hz). The coupling constant of H-2 (*J*=6.5 Hz) suggested trans relationship between H-2 and H-3 which is characteristic for catechin [13]. In the HMBC spectrum of **3**, long range correlations between C(6) 95.5 ppm and H-

4a (δ_H 2.41) was observed. From these data, the structure of compound **3** was established as (-)-8-chlorocatechin. We also first reported natural halogenated flavan-3-ol (6-chlorocatechin) from *Rumex patientia* (Polygonaceae) [14].

Table 2. ^{1}H- and ^{13}C-NMR data[a)] and HMBC correlations of **2.**(in CD_3OD; in ppm, *J* in Hz)

Atom	**2**		
	δ (H)[b)]	δ (C)[c)]	HMBC (H→C)
Aglycone			
C(1)		36.5	
CH_2(2)	1.22 (*t, J*=12.0)	47.8	C(1), C(3), C(4), C(12)
			C(3), C(4), C(6)
	1.88*		
H-C(3)	3.87 *	75.9	
CH_2(4)	1.05 *	43.7	C(3), C(5), C(6), C(13)
			C(13)
	2.19 *		
H-C(5)	1.76 (*m*)	32.1	
H-C(6)	1.58 (*t, J*= 10.5)	59.2	C(1), C(5), C(7), C(8),
			C(11)
H-C(7)	6.66 (*dd, J*= 5.5, 15.8)	151.9	C(5), C(9)
H-C(8)	6.08 (*d, J*= 15.8)	134.7	C(6), C(9), C(10)
C(9)		201.0	
Me(10)	2.26 (*s*)	27.1	C(7), C(8), C(9)
Me(11)	0.95 (*s*)	21.9	C(2), C(3), C(6), C(12)
Me(12)	0.89 (*s*)	31.9	C(2), C(3), C(6), C(11)
Me(13)	0.84 (*d, J*= 6.5)	21.8	C(4), C(5), C(6)
Sugar			
H-C(1')	4.35 (*d, J*= 7.5)	103.1	C(3), C(3')
H-C(2')	3.13 (*dd, J*= 7.5, 9.3)	75.2	C(1'), C(4')
H-C(3')	3.34 (*t, J*= 9.1)	78.2	C(2'), C(4')
H-C(4')	3.25 (*t, J*= 9.5)	71.9	C(2'), C(3') C(6')
H-C(5')	3.42 (*t, J*= 9.8)	76.9	
H-C(6')	3.61*	68.8	C(1'')
	3.97*		C(1''), C(4')
H-C(1'')	5.02 (*d, J*= 2.5)	111.1	C(6'), C(3''), C(4'')
H-C(2'')	3.89 (*d, J*= 2.5)	78.2	C(1''), C(5''),
C(3'')		80.7	
CH_2(4'')	3.77*	75.2	C(1''), C(2''), C(3'')
	3.98		C(1''), C(3''), C(5'')
CH_2(5'')	3.59 (*s*)	65.8	C(2''), C(4'')
	3.59 (*s*)		C(2''), C(4'')

[a]All δ (H) and δ_C assignments are based on 2D NMR (DQF-COSY, HMQC, HMBC).
[b]Recorded at 500 MHz.
[c]Recorded at 125 MHz
*Overlapping signals. Arbitrary atom numbering

The known metabolites, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one (**4**) [15] and 3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-propan-1-one (**5**) [16], *trans*-resveratrol-3-O-*β*-glucopyranoside (**6**) [17] lyoniresinol-9-O-*β*-xylopyranoside (**7**) [18], lyoniresinol-9-O-*β*-glucopyranoside (**8**) [19]) were identified by comparing their 1D- and 2D-NMR spectral data those were published in the literature.

To the best of our knowledge, the presence of a megastigmane glycoside in genus *Quercus* was reported for the first time in this article. Since megastigmanes are aroma compounds and oak barrels are one of the factor to effect to wine content, it can be an interesting project focus on megastigmanes of *Quercus*.

Table 3. ^{1}H- and ^{13}C-NMR Data[a)], and HMBC correlations for **3**. (in CD_3OD; in ppm, *J* in Hz)

Atom	**3**		
	δ (H)[b)]	δ (C)[c)]	HMBC (H→C)
Aglycone			
H-C(2)	4.69 (*d, J*= 6.5)	81.1	C(3), C(8a), C(1'), C(2'), C(6')
H-C(3)	3.89 *	65.7	
CH_2(4)	2.41 (*dd, J*= 7.3, 16.2)	27.1	C(2), C(3), C(4a), C(5)
	2.59 (*dd, J*= 5.2, 16.2)		C(2), C(3), C(4a)
C(5)		154.0	
H-C(6)	6.15 (*s*)	95.5	C(4a), C(5), C(7), C(8)
C(7)		152.0	
C(8)		97.6	
C(9)		150.5	
C(10)		100.3	
C(1')		130.1	
H-C(2')	6.71 (*d, J*= 1.7)	114.2	C(2), C(3'), C(4')
C(3', 4')		144.9	
H-C(5')	6.69 (*d, J*= 8.0)	115.2	C(1'), C(3'), C(4') C(6')
H-C(6')	6.58 (*dd, J*= 1.7, 8.0)	118.0	C(2), C(3'), C(4')

[a]All δ (H) and δ_C assignments are based on 2D NMR (DQF-COSY, HMQC, HMBC).
[b]Recorded at 500 MHz.
[c]Recorded at 125 MHz, Arbitrary atom numbering.
[*]Overlapping signals. Arbitrary atom numbering.

Acknowledgments

The authors would like to thank Pharmacist İsa Arı (Mut/Mersin) for sample collection.

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