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New lignan glycosides from *Cissus quadrangularis* stems

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ABSTRACT

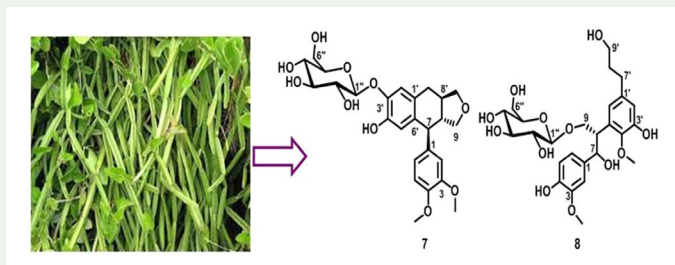
Phytochemical investigation of *Cissus quadrangularis* stems led to the isolation of one new phenolic glycoside (**1**) and two new lignan glycosides (**7** & **8**) along with twelve known compounds (**2–6** & **9–15**). Their chemical structures were determined on the basis of extensive spectroscopic analysis using 1D, 2D NMR, and mass spectrometric analysis. Among the known compounds, **4–6**, **9** and **12** were isolated for the first time from the genus *Cissus* whereas compounds **10**, **11** and **13** for the first time from this plant.

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1. Introduction

Cissus quadrangularis (Vitaceae), a home garden plant commonly known as ‘Hadjod’ in hindi due to its bone joining activity (Prasad and Udupa 1964), is widely distributed throughout tropical and subtropical regions of the world such as India, Sri Lanka, South Africa, Thailand, Java, and Philippines (Teppner 2003). In Ayurveda, its use is mentioned for the treatment of various ailments such as weight management and bone related disorders. It has also wide application in osteoporosis (Kumar et al. 2010), in complains of back and spine (Asolkar et al. 1999). The previous phytochemical investigations showed the presence triterpenes

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(Bhutani et al. 1984), stilbene and flavonoids (Adesanya et al. 1999) and iridoids (Singh et al. 2007).

As a part of our ongoing phytochemical research interest of medicinal plants, we investigated the stems of *C. quadrangularis* which lead to the isolation of one new phenolic glycoside (**1**) and two new lignan glycosides (**7** & **8**) along with twelve known compounds (**2–6** & **9–15**) of different class.

2. Results and discussion

The shade dried stems of *C. quadrangularis* was extracted with 95% ethanol, which was successively fractionated with *n*-hexane, *n*-butanol and water. The isolation was performed by use of different chromatographic methods. Among the isolated fifteen compounds (Figure 1), a new phenolic glycoside, cissusic acid (**1**) and two new lignan glucosides, cissuside (**7**) and cissusol (**8**), and twelve known compounds, quercetin-3-O- α -rhamnopyranoside (**2**) (Rodrigues et al. 2009), (6*R*)-9,10-dihydroxy-4,7-megastigmadiene-3-one-9-O- β -D-glucopyranoside (**3**) (Saleem et al. 2006), (6*R*)-6,9-dihydroxy-4,7-megastigmadiene-3-one-9-O- β -D-glucopyranoside (**4**) (Cuong et al. 2009), (6*R*)-6,9,10-trihydroxy-4,7-megastigmadiene-3-one-9-O- β -D-glucopyranoside (**5**) (Matsunami et al. 2010), cimidaurine (**6**) (Kanemoto et al. 2008), cuminaldehyde (**9**) (Lee 2005), vanilline (**10**) (Valente et al. 2004) and eugenol (**11**) (Sathyaprabha et al. 2010), (-)- β -caryophyllene oxide (**12**) (Ragasa et al. 2003), β -amyrone (**13**) (Li et al. 2008), cholest-4-ene-3-one (**14**) (Parish et al. 1991), and β -sitosterol (**15**) (Ramadan et al. 2009), characterised with the help of spectroscopic and chemical properties. The known compounds were characterised by

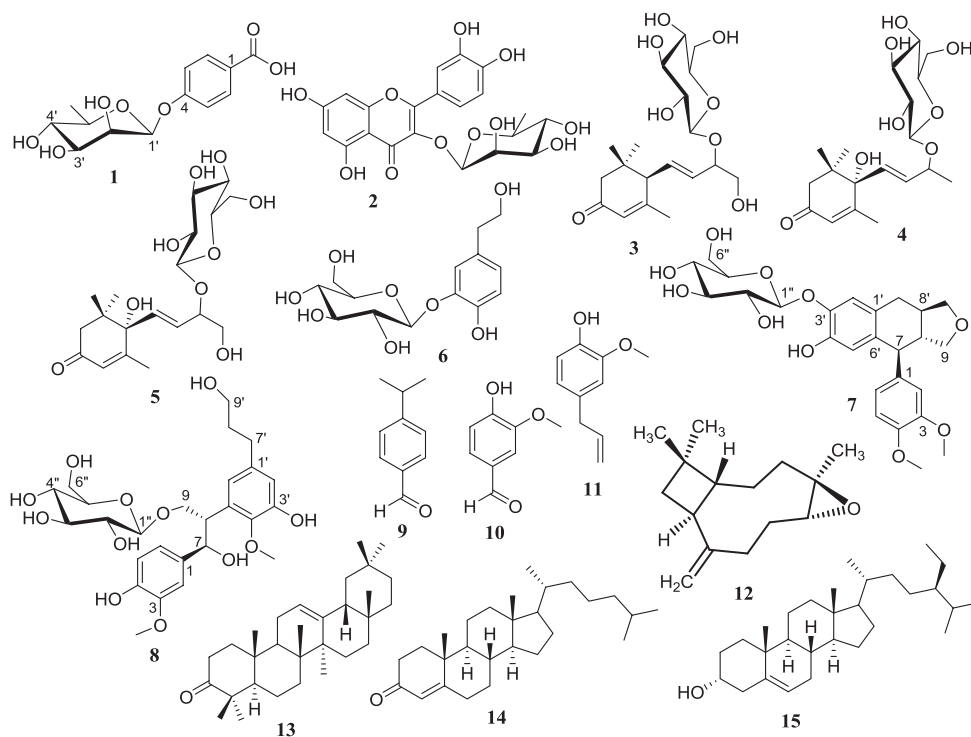


Figure 1. Chemical structure of isolated compounds (1–15).

comparing NMR data with those reported in the literature. Among known compounds, **4–6**, **9** and **12** were isolated for the first time from the genus *Cissus* whereas compounds **10**, **11** and **13** for the first time from this plant.

2.1. Structure elucidation

Compound **1** was isolated as light yellow sticky with molecular formula (m. f.) of $C_{13}H_{16}O_7$ by HR-MS. The structure of compound **1** was confirmed by detailed analysis of 1D and 2D NMR spectral analysis (Table S1). A disubstituted aromatic ring was evidenced by four methine protons at δ_H 6.93 (2H, d, $J = 8.7$ Hz) and δ_H 7.75 (2H, d, $J = 8.1$ Hz) with their corresponding carbon signals at δ_C 115.0 (C-3, C-5) and 130.4 (C-2, C-6), respectively (Fiorentino et al. 2008) confirmed by HSQC experiment. Three quaternary carbon signals were appeared at δ_C 178.0 corresponding to acid carbonyl group (Aquino et al. 2002), 121.1 (C-1) and 160.1 (C-4). The 1H and ^{13}C NMR spectra also showed the presence of a rhamnose sugar unit, attached through a 1'→4 linkage to the 4-hydroxyl benzoic acid unit confirmed by HMBC spectral data (Figure S1). The coupling constant ($J = 7.6$ Hz) of the anomeric proton (δ_H 5.37, H-1' and δ_C 102.0, C-1') indicated that sugar moiety was connected with aromatic ring via a β -linkage. A doublet of three proton at δ_H 0.92 (3H, d, $J = 4.7$ Hz', H-6') with its carbon signal at δ_C 16.7 (C-6') confirmed the presence of rhamnose sugar. Therefore, the structure of compound **1** was assigned as 4-(β -rhamnopyranosyloxy) benzoic acid trivially named as cissusic acid.

Compound **7** was isolated as brown sticky with m. f. $C_{26}H_{32}O_{10}$ by HR-MS analysis. The structure of compound **7** was inferred from the detailed analysis of 1H and ^{13}C along with 2D NMR (Table S2) and CD experiments (Figure S37). 1H -NMR and 1H - 1H COSY spectra indicated the presence of a 1,3,4-trisubstituted benzene ring and another 1',3',4',6'-tetrasubstituted benzene ring. The presence of two signals of methoxy group at δ_H 3.79 (3H, s, OMe-4), 3.80 (3H, s, OMe-3), three methylene signal at δ_H 2.82 (2H, m, H-7'), 3.73 (2H, m, H-9'), and 4.07 (1H, dd, $J = 10.8, 6.5$ Hz, H_a -9), 3.24 (1H, m, H_b -9), three methine signal at δ_H 1.85 (1H, m, H-8'), 4.05 (1H, m, H-8), 2.07 (1H, brs, H-7) in aglycon moiety, indicating the existence of aryltetralin lignan scaffold. For glucose moiety, 1H NMR showed four methine signals at δ_H 3.29–4.08 (4H, m, H-2''–H-5''), one methylene at δ_H 3.84 (1H, d, $J = 5.7$ Hz, H_a -6''), 3.64 (1H, dd, $J = 11.6, 5.5$ Hz, H_b -6'') and a anomeric methine signal at δ_H 4.12 (1H, d, $J = 7.9$ Hz, H-1''), showing β -glucopyranosyl unit. ^{13}C NMR showed twenty-six carbon signals of which twelve aromatic carbons with two methoxy groups, three methylene carbons, and three aliphatic methine carbons. The position of substituents was confirmed by HMBC correlations. In the HMBC spectral data, cross peak observed between H-1'' with C-3', confirmed the position of sugar at C-3' and cross peaks at δ_H 3.80 (OMe-3) with C-3, δ_H 3.79 (OMe-4) with C-4 showed the existence of 3, 4-dimethoxyphenyl ring. Other correlation in HMBC spectrum showed cross peaks between H-2' and C-1', C-4', C-6', H-5' and C-1', C-3', H-7 and C-1', C-2, C-5', H-5 and C-1, C-3 (Kim et al. 1994). The relative and absolute spatial arrangement was confirmed on the basis of analysis of NOESY and circular dichroism (CD) experiments. Klyne (Klyne et al. 1966) reported that 4 α -aryl (7R) lignan afforded positive cotton effect around 280–290 nm, while 4 β -aryl (7S) shows negative cotton effect in CD spectrum. Consequently, compound **7** showed negative cotton effect at 290 nm and positive cotton effect at 273 nm. Hence, the absolute configuration for C-7 was assigned as *S* (He et al. 2004). The absence of NOESY correlation between H-8' and H-8 indicates that they are in *trans* configuration.

Therefore, the absolute configuration of C-8' and C-8 were assigned to both *R* (Iida et al. 2010). Based on these evidences, the absolute configuration of compound **7** was determined to be (8'*R*, 8*R*, 7*S*). Hence, the compound **7** was characterised and named as cissuside.

Compound **8** was obtained as yellowish sticky with m.f. C₂₆H₃₆O₁₂ by HRMS analysis. The structure of compound **8** was confirmed from the detailed analysis of ¹H and ¹³C along with 2D NMR (Table S3) and CD (Figure S47) experiments. The ¹H NMR spectra exhibited one set of 1,3,4-trisubstituted aromatic hydrogens, and one set of tetrasubstituted aromatic protons, two signal of methoxy group at δ_{H} 3.84 (3H, *s*, MeO-3), 3.87 (3H, *s*, MeO-4'), four methylene signal at δ_{H} 4.23 (2H, *m*, H-9), 2.64 (2H, *t*, *J* = 7.8 Hz, H-7'), 1.83 (2H, *m*, H-8'), 3.58 (2H, *t*, *J* = 6.4 Hz, H-9'), two methine signals at δ_{H} 5.61 (1H, *d*, *J* = 6.1 Hz, H-7), 3.65 (1H, *m*, H-8) and ¹³C NMR showed twenty aromatic carbons with two methoxy groups, four methylene carbons, and two aliphatic methine carbons corresponding to aglycon moiety. For glucose moiety, ¹H NMR showed four methine signals at δ_{H} 3.29–3.67 (4H, *m*, H-2''–H-5''), one anomeric methine signal at δ_{H} 4.37 (1H, *d*, *J* = 7.7 Hz, H-1''), showing β -glucopyranosyl unit, and one methylene signal at δ_{H} 3.67 (2H, *d*, *J* = 12.0 Hz, H-6'') with their corresponding carbon signals at δ_{C} 73.7 (C-2''), 76.8 (C-3''), 70.2 (C-4''), 76.6 (C-5''), 103.1 (C-1'') and 61.4 (C-6''). The position of substituents was confirmed by HMBC correlations. In HMBC spectrum, the anomeric proton at δ_{H} 4.37 (Iida et al. 2010) showed correlation with C-9, indicates that the position of sugar at C-9 and the cross peak at δ_{H} 5.61 showed correlations with C-2, C-6 and δ_{H} 3.65 showed correlations with C-9, C-4' indicates the connectivity of both the phenyl rings at C-7 and C-8, respectively. The proton at δ_{H} 2.64 showed correlations with C-1', C-2', C-6', C-8', C-9' indicated that the presence of propanol side chain at C-1' position of aromatic ring. The structure was further supported by the COSY correlation between H-7–H-8 and H-8–H-9. Establishment of relative and absolute configuration was based on the NOESY and CD experiments. The absence of correlation between H-7 and H-8 in NOESY spectra indicates that H-7 and H-8 have *trans* configuration. The absolute configurations of C-7 and C-8 were confirmed as *R* and *S*, respectively from CD spectrum analysis which showed the positive cotton effect at 254 nm and the negative cotton effect at 294 nm (Hosup et al. 2004). Hence, the compound **8** was characterised and named as cissusol.

3. Conclusion

In conclusion, the phytochemical investigation of the methanol extract of *Cissus quadrangularis* stems yielded three new compounds along with twelve known compounds. Among three new compounds, one compound belongs to the phenolic glycoside (**1**) whereas remaining two from lignan glycosides (**7** & **8**). This study reveals the type of compounds presents in *Cissus quadrangularis*. These compounds belong to different categories such as phenolics, terpenes, steroids and flavonoids.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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