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Insecticidal and α-glucosidase inhibitory activities of chemical constituents from *Viburnum fordiae* Hance

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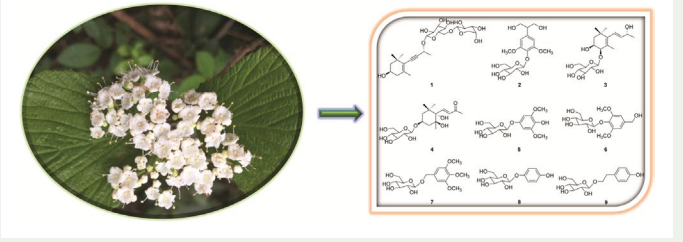
ABSTRACT

The ethanolic extract of the stems of *Viburnum fordiae* Hance showed insecticidal and α-glucosidase inhibitory activities and then was fractionated by bioactivity-guided fractionation to obtain a rare C_{13}-norisoprenoid (**1**), together with a new phenolic glycoside (**2**), and seven known compounds, alangionoside C (**3**), pisumionoside (**4**), koaburaside (**5**), 3,5-dimethoxy-benzyl alcohol 4-*O*-β-D-glucopyranoside (**6**), 3,4,5-trimethoxybenzyl-β-D-glucopyranoside (**7**), arbutin (**8**), and salidroside (**9**). The previously undescribed compounds were elucidated as (3*R*,9*R*)-3-hydroxy-7,8-didehydro-β-ionyl 9-*O*-α-D-arabinopyranosyl-(1→6)-β-D-glucopyranoside (**1**) and 2-(4-*O*-β-D-glucopyranosyl)syringylpropane-1,3-diol (**2**) by spectroscopic data (^{1}H and ^{13}C NMR, HSQC, HMBC, ^{1}H-^{1}H COSY, HSQC-TOCSY, HRESIMS, IR and ORD) and chemical methods. Compound **1** showed potent insecticidal effect against *Mythimna separata* with LD_{50} value of 140 μg g^{-1}. Compounds **2**, **5**, **6**, **8** and **9** showed varying α-glucosidase inhibitory activity with IC_{50} values ranging from 148.2 to 230.9 μM.



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1. Introduction

Many species of *Viburnum*, belonging to the family Adoxaceae (formerly Caprifoliaceae), have attracted attention as garden or landscape plants because of their showy flowers and

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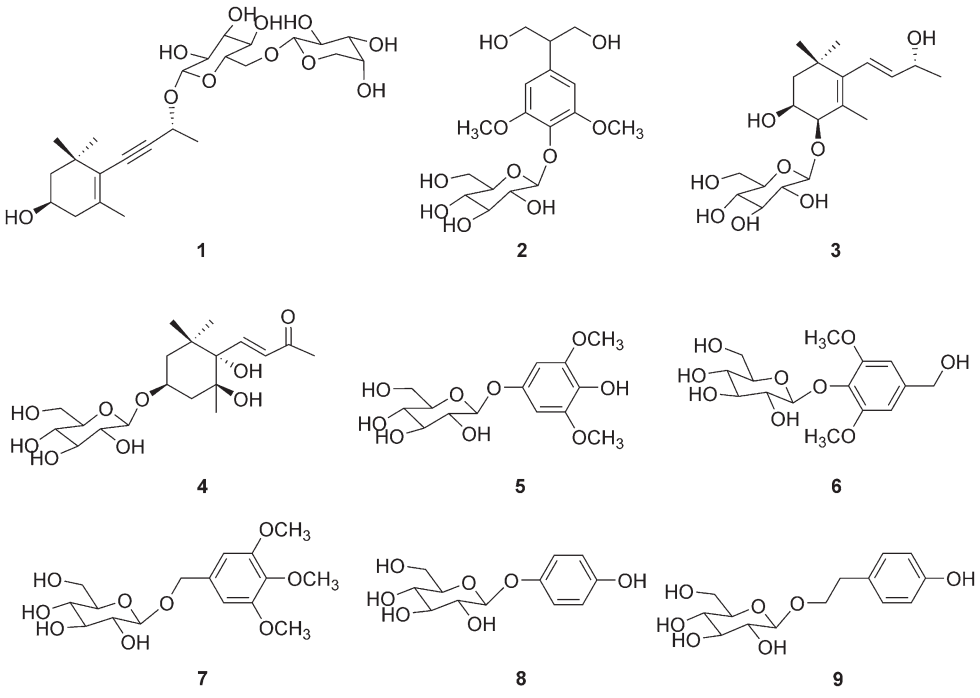

Figure 1. The structures of compounds **1**–**9**.

berries. More importantly, they have notable biological activities that can improve human health and treat various diseases (El-Gamal 2008; Seeram 2008; Saltan et al. 2016). Previous phytochemical and pharmacological investigations on *Viburnum* species clearly indicated that these plants contain monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, iridoids, lignans, flavonoids and other phenolic compounds, some of which possessed antitumor, antimicrobial, antioxidant, antihyperglycemic, anti-inflammatory and neuroprotective activities (Wang et al. 2010; In et al. 2015). *Viburnum fordiae* Hance is a small tree widely distributed in the south of China. As a common traditional Chinese medicine, its stems have been used for the treatment of rheumatic arthralgia and allergic dermatitis (Zhonghuabencao Editorial Board 1999). The crimson fruits of *V. fordiae*, ripening in autumn, have also been reported as a promising functional food (Shao et al. 1992). To the best of our knowledge, there were minimal work on the chemical constituents and biological activities focusing on *V. fordiae*. As part of our continuing search for bioactive constituents from the genus *Viburnum* (Shao et al. 2018), we investigated the ethanol extract from the stems of *V. fordiae*. Nine compounds were isolated from its *n*-butanol fraction (Figure 1). Among them, two previously undescribed compounds (**1**, **2**) have been unambiguously determined by extensive spectroscopic methods, including 1D (^{1}H and ^{13}C) and 2D NMR (HSQC, HMBC, ^{1}H-^{1}H COSY, and HSQC-TOCSY), IR and HRESIMS, and chemical transformations. The insecticidal and *α*-glucosidase inhibitory activities of all isolated secondary metabolites were assayed. Herein, we describe the isolation, structural elucidation and evaluation of insecticidal and *α*-glucosidase inhibitory activities of these compounds.

2. Results and discussion

Compound **1** was isolated and purified as white amorphous power. Its positive HRESIMS spectrum exhibited a sodium adduct molecular ion peak $[M + Na]^+$ at *m/z* 525.2321 (Calcd 525.2306), corresponding to the molecular formula $C_{24}H_{38}O_{11}$ with 6° of unsaturation. The IR spectrum indicated the presence of alkyne (ν_{max} 2209 cm^{-1}) and alkene (ν_{max} 1623 cm^{-1}) groups. The ^1H NMR spectrum of **1** (Table S1, Supplementary material) displayed proton signals corresponding to two oxygenated methine groups at δ_H 3.72 (1H, m, H-3) and 4.78 (1H, q, J = 6.5 Hz, H-9), two methylene moieties at δ_H 1.26 (1H, t, J = 12.1 Hz, H-2ax), 1.69 (1H, ddd, J = 12.1, 3.7, 2.1 Hz, H-2 eq), 1.90 (1H, dd, J = 17.5, 9.7 Hz, H-4ax) and 2.25 (1H, dd, J = 17.5, 5.6 Hz, H-4 eq), four methyl residues at δ_H 1.05 (3H, s, H-11), 1.09 (3H, s, H-12), 1.40 (3H, d, J = 6.5 Hz, H-10) and 1.80 (3H, s, H-13). Combining with HSQC spectrum of **1**, the ^{13}C NMR spectrum showed 13 signals of aglycone, assigned to four methyl groups at δ_C 22.2 (C-13), 22.5 (C-10), 28.4 (C-11) and 30.3 (C-12), two methylene moieties at δ_C 41.1 (C-4) and 46.4 (C-2), two oxygenated methine groups at δ_C 62.5 (C-3) and 62.6 (C-9) and five quaternary carbons at δ_C 35.9 (C-1), 83.1 (C-7), 92.7 (C-8), 122.5 (C-6) and 138.3 (C-5). The above data, together with 6° of unsaturation, implied that compound **1** should be a C_{13}-norisoprenoid (Cutillo et al. 2005; Picerno et al. 2008). Acid hydrolysis of **1** resulted in liberating D-glucose and D-arabinose, which were analysed by TLC, ORD and GC, and the configuration of the pentose was determined by Hara's method (Hara et al. 1987; Seo et al. 2002; Sun et al. 2016). The D-glucose and D-arabinose were confirmed to have β- and α-linkages by the coupling constants of anomeric protons at δ_H 4.43 (1H, d, J = 7.8 Hz, H-1′) and 4.17 (1H, d, J = 6.2 Hz, H-1″), respectively (Pei et al. 2011). In the HMBC spectrum of **1** (Figure S16, Supplementary material), key correlations from H-10 (δ_H 1.40) to C-9 (δ_C 62.6) and C-8 (δ_C 92.7), from H-9 (δ_H 4.78) to C-8 and C-7 (δ_C 83.1), from H-2 (δ_H 1.26, 1.69) and H-4 (δ_H 1.90, 2.25) to C-3 (δ_C 62.5), and from H-13 (δ_H 1.80) to C-5 (δ_C 138.3) and C-6 (δ_C 122.5) indicated that two oxygenated groups, an alkynyl moiety, and an alkenyl residue were substituted at C-9, C-3, C-7 and C-5 positions, respectively. Also, the correlations of H-1′ (δ_H 4.43) with C-9 (δ_C 62.6) and H-1″ (δ_H 4.17) with C-6′ (δ_C 64.8) indicated that the linkage points of the glucose and arabinose units were at C-9 and C-6′, respectively. Based on the above data and comprehensive 2D NMR experiments (^1H-^1H COSY, HSQC-TOCSY and HMBC), the structure of **1** was unambiguously assigned as shown in Figure 1. According to the literature, in the ^{13}C NMR spectra of **1** in D_2O (Table S1, Supplementary material), the chemical shift (δ_C 68.2) of C-9 indicated that the absolute configuration of C-9 was *R* (Yamano et al. 2002). The relative stereochemistry at C-3 in the aglycone group of **1** was identified by a large coupling constant of H-4ax (J = 9.7 Hz). This implied that H-3 must be in the axial position (Yue et al. 2012). C_{13}-norisoprenoids are biosynthetically formed in nature from the hydrolytic breakdown of complex secondary metabolites derived from carotenoids which have *R*-configuration for C-3 (Yamano et al. 2000; Baumes et al. 2002; Yamano et al. 2002). Thus, compound **1** was determined as (3*R*,9*R*)-3-hydroxy-7,8-didehydro-β-ionyl 9-*O*-α-D-arabinopyranosyl-(1→6)-β-D-glucopyranoside.

Compound **2**, white amorphous powder, had the molecular formula $C_{17}H_{26}O_{10}$ as deduced by analysis of positive HRESIMS (*m/z* 413.1442 $[M + Na]^+$, Calcd 413.1418). Hydrolysis of **2** with β-glucosidase produced an aglycone and β-D-glucose, which was identified by the positive optical rotation $[\alpha]_D^{23} = +48.6$ (*c* 0.2, H_2O) (Jiang et al. 2015). The ^1H NMR spectrum of **2** (Table S2, Supplementary material) indicated the presence of a 1,3,4,5-tetrasubstituted benzene ring residue [δ_H 6.52 (2H, s, H-2′, 6′)], two methoxyl groups [δ_H 3.74 (6H, s, -OC$\underline{H}_3$-3′,

5′)], and a propane chain [two methylene moieties at δ_H 3.58 (2H, m, H-1, 3), 3.67 (2H, m, H-1, 3) and a methine group at δ_H 2.72 (1H, m, H-2)]. Combining with HSQC spectrum of **2**, this aliphatic part was further confirmed in the ^{13}C NMR spectrum by a methine carbon signal at δ_C 50.7 (C-2) and a methylene peak at δ_C 62.7 (C-1 and C-3). Considering only 7 carbon resonances corresponding to the aglycone in the ^{13}C NMR spectrum together with the above molecular formula, it was obvious that the aglycone of compound **2** should possess a symmetrical structure. The structure of **2** was further determined by HMBC experiment. Key HMBC correlations from H-1″ (δ_H 4.83) to C-4′ (δ_C 133.2), from H-2 (δ_H 2.72) to C-1′ (δ_C 137.9), C-2′ (δ_C 106.7) and C-6′ (δ_C 106.7), and from H-1 (δ_H 3.58, 3.67) and H-3 (δ_H 3.58, 3.67) to C-1′ showed the linkage points of glucosyl unit and syringyl group, respectively. Consequently, compound **2** was identified as 2-(4-*O*-*β*-D-glucopyranosyl)syringylpropane-1,3-diol.

Compounds **3**–**9**, by comparing the physical and spectral data with literature values (Experimental Section, Supplementary material), were determined as alangionoside C (**3**), pisumionoside (**4**), koaburaside (**5**), 3,5-dimethoxy-benzyl alcohol 4-*O*-*β*-D-glucopyranoside (**6**), 3,4,5-trimethoxybenzyl-*β*-D-glucopyranoside (**7**), arbutin (**8**) and salidroside (**9**).

The *n*-butanol soluble fraction of *V. fordiae* was initially assayed for its insecticidal and *α*-glucosidase inhibitory activities (Experimental Section, Supplementary material). The obtained data of bioassay revealed that the *n*-butanol extract showed the moderate insecticidal activity against *Mythimna separata* Walker with LD_{50} value of 297 μg g^{-1} and *α*-glucosidase inhibitory activity with IC_{50} value of 258 μg mL^{-1}. Subsequently, the *n*-butanol extract was isolated and purified by chromatographic methods to give nine compounds (**1**–**9**). These compounds were further tested for insecticidal and *α*-glucosidase inhibitory activities. New compound **1** showed potent insecticidal effects against *M. separata* with LD_{50} value of 140 μg g^{-1} in comparison with isonimbinolide (124 μg g^{-1}) and celangulin-V (312 μg g^{-1}), while compounds **3** and **4** were inactive. This might be attributed to the existence of an alkynyl unit at C-7 of **1**. Among the tested phenolic compounds, **2**, **5**, **6**, **8** and **9** exhibited potent intestinal *α*-glucosidase inhibitory activity with IC_{50} values ranging from 148.2 to 230.9 μM in comparison to the positive control acarbose (IC_{50} = 220.4 μM) (Figure S18, Supplementary material), while **7** did not show inhibitory effect. This result preliminarily indicated that the free hydroxyl group in aglycone played a key role in exerting inhibition of *α*-glucosidase. Postprandial hyperglycemia (PPHG), treated by *α*-glucosidase inhibitors via delaying the digestion of carbohydrates in the intestines, is involved in the development of type 2 diabetes (Yao et al. 2010). Obviously, the obtained data of the bioactivity assays indicated that *V. fordiae* Hance containing these constituents could be developed as drugs to treat type 2 diabetes and insecticidal agents.

3. Conclusions

The ethanol extract of *V. fordiae* exhibited insecticidal and *α*-glucosidase inhibitory activities, which suggested the potential presence of bioactive secondary metabolites. Bioassay guided fractionation and purification obtained two new compounds (**1**, **2**) and seven known compounds (**3**–**9**). Compounds **3**, **4**, **6**, and **7** were found for the first time in genus *Viburnum*. In bioactivity assays, compound **1** showed potent insecticidal activity against *M. separata*, and **2**, **5**, **6**, **8** and **9** showed potent *α*-glucosidase inhibitory activity. In conclusion, these results provided initial evidence of *V. fordiae* with implication towards potential insecticidal and *α*-glucosidase inhibitory properties.

Supplementary material

Experimental details, MS, IR and NMR spectra, and data of bioactivity assays are available alongside Figures S1–S18 as well as Tables S1 and S2, respectively.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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