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Chemical constituents from *Valeriana officinalis* L. var. Iatifolia Miq. and their chemotaxonomic significance

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ABSTRACT

Twenty-one compounds, including four monoterpenoids (**1**–**4**) (two new natural products, **1** and **2**), four sesquiterpenes (**5**–**8**), two iridoids (**9** and **10**), four steroids (**11**–**14**), five phenolic compounds (**15**–**19**), and two alkaloids (**20** and **21**), were isolated from the roots of *Valeriana officinalis* L. var. Iatifolia Miq. Their chemical structures were established by spectroscopic methods and further confirmed by comparison with published data in the literature. Among them, eight compounds (**1**, **2**, **6**–**8**, **13**, **18**, and **21**) are being reported from the family Valerianaceae for the first time, and compounds **9**–**12** were obtained from *V. officinalis* for the first time. The chemotaxonomic significance of the isolated compounds is discussed.

1. Subject and source

The genus *Valeriana* consists of approximately 200 species mainly distributed in Europe, Asia, and North America (Piccinelli et al., 2004), and 17 species are found in China (Editorial Committee of Chinese Flora, 1986). *Valerian* is a perennial herb, and some species in this genus have been widely used as a mild sedative and sleep aid for centuries. *Valeriana officinalis* L. var. Iatifolia Miq. is abundantly distributed in mainland China, and the roots of this plant have been used in traditional Chinese folk medicine for the treatment of insomnia for centuries in many parts of China, especially in Guizhou, Yunnan, and Sichuan provinces (Houghton, 1988; Chen and Cheng, 1994).

In the present study, the roots of *V. officinalis* were collected in Tongren, Guizhou Province, China, and were identified by Dr. Mingjin Huang. A voucher specimen (H20170708) was deposited in the Key Laboratory of Chemistry for Natural Products of Guizhou Province and Chinese Academy of Science.

2. Previous work

Previous phytochemical investigations of *V. officinalis* resulted in the isolation of various sesquiterpenes (Wang et al., 2010, 2011b, 2016; Han et al., 2015), iridoids (Xie et al., 2019), lignans (Wang et al., 2011a), and alkaloids (Torssell and Wahlberg, 1966).

3. Present study

The air-dried and powdered roots of *V. officinalis* (30 kg) were refluxed with 95% ethanol (3 × 50 L) for three times (3 × 3 h). The combined extract was concentrated under reduced pressure by a rotary evaporator to obtain the residue (5.0 kg). The extract was suspended in water and then partitioned with EA (ethyl acetate) (4 × 10 L). The ethyl acetate portion (926 g) was applied to a silica gel column, and PE (petroleum ether)/EA gradient elution (50:1 to 1:1) was used to afford ten fractions (Fr.1–Fr.10). Fr.2 (57.2 g) was separated on a silica gel column eluted with PE/acetone (50:1 to 1:1) to give **15** (24 mg), **16** (11 mg), and **17** (5 mg). Fr.3 (17.6 g) was subjected to column chromatography over silica gel eluted with PE/EA (50:1 to 1:1) and further separated on Sephadex LH-20 to afford **1** (9 mg), **2** (7.2 mg), **3** (100 mg), and **4** (11 mg). Fr. 4 (15.6 g) was repeatedly chromatographed over silica gel and eluted with PE/acetone (100:1 to 9:1) to obtain **5** (36 mg), **6** (1.6 mg), **7** (4.5 mg), and **11** (55 mg). Fr.5 (35.4 g) was applied to an MCI gel column and eluted with a gradient CH_3OH/H_2O (50:50 to 95:5) to yield five fractions (Fr.5A–Fr.5G). Fr. 5D (5.2 g)

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was separated by column chromatography over silica gel and further separated by semi-preparative HPLC with an X-bridge column eluted with CH_3OH/H_2O (2.0 mL/min, $CH_3OH:H_2O$ = 65:35, v/v) to yield **9** (17 mg, t_R = 31 min), **10** (36 mg, t_R = 47 min), **12** (19 mg, t_R = 54 min), **8** (4 mg, t_R = 56 min), and **13** (17 mg, t_R = 60 min). Fr.8 (46.2 g) was subjected to column chromatography over silica gel eluted with dichloromethane/acetone (100:1 to 1:1) and further separated on Sephadex LH-20 to obtain **14** (100 mg), **18** (50.2 mg), **19** (43 mg), **20** (61 mg), and **21** (7 mg).

The structures of these compounds were elucidated on the basis of extensive NMR experiments, HR-ESI-MS analysis, and comparison with published data in the literature. A total of 21 compounds, including four monoterpenoids (**1–4**) (two new natural products, **1** and **2**), four sesquiterpenes (**5–8**), two iridoids (**9** and **10**), four steroids (**11–14**), five phenolic acids (**15–19**), and two alkaloids (**20** and **21**), were determined to be (−)-5-exo-acefoxybornyl acetate (**1**) (Allen et al., 2011), (1*R*,2*S*,4*R*,5*R*)-5-hydroxy-1,7,7-trimethylbicyclo [2.2.1]heptan-2-yl acetate (**2**) (Acerson et al., 2015), borneol (**3**) (Perry et al., 1996), bornyl acetate (**4**) (Jung Wook et al., 2009), kissoone A (**5**) (Wang et al., 2015), 3,11-dihydroxy-3,7,11-trimethyldodeca-1,6,9-triene (**6**) (Stoessl et al., 1975), 9-oxonerolidol (**7**) (Iida et al., 1982), 12-hydroxy-*β*-caryophyllene-4,5-oxide acetate (**8**) (Williams et al., 1997), rupesin B (**9**) (Yang et al., 2006), jatamanvaltrate P (**10**) (Yang et al., 2015), stigmast-4-en-3-one (**11**) (Yuan et al., 2008), 6-hydroxystigmast-4-en-3-one (**12**) (Anjaneyulu et al., 1989), 7-oxo-*β*-sitosterol (**13**) (Zhang et al., 2005), *β*-sitosterol (**14**) (Zhai and Liu, 2015), benzoic acid (**15**) (Huang et al., 2016), *trans*-cinnamic acid (**16**) (Yang et al., 2000), phthalate (**17**) (Wang et al., 2013), 2-methoxy-4-(3-methoxy-l-propenyl)-phenol (**18**) (Naito et al., 1992), (+)-prinsepiol (**19**) (Kilidhar et al., 1982), (−)-actinidine (**20**) (Beckett et al., 2010), and indole-3-carbaldehyde (**21**) (Zhou et al., 2010) (Fig. 1).

Compound **1** had the molecular formula $C_{14}H_{22}O_4$ based on HR-ESI-MS (*m/z* 277.1407, [M + Na] + , calcd for $C_{14}H_{22}O_4$ 277.1410) analysis. Analysis of its ^{1}H NMR spectrum showed five methyl proton signals and two signals indicative of oxygenated methine protons. The ^{13}C NMR and DEPT spectra (Table 1S) of **1** exhibited 14 carbon signals, including five methyls, two methylenes, three methines (two oxygenated carbons), and four quaternary carbons (two ester carbonyls). In the ^{1}H–^{1}H COSY spectrum, cross-peaks of H-2/H_2-3, H_2-3/H-4, and H-5/H_2-6 constructed two structural fragments. In the HMBC spectrum (Fig. 2), the key correlations from Me-8 to C-1, C-2, C-6, and C-7; from H-4 to C-3, C-5, and C-7; and from gem-methyls Me-9 and Me-10 to C-1, C-4, and C-7 indicated the existence of a bicyclo [2.2.1]heptane moiety. In addition, two acetyl groups were attached at C-2 and C-5, which could be easily demonstrated by the HMBC cross-peaks of H-2 and Me-12 to C-11 and of H-5 and Me-14 to C-13. Therefore, the planar structure was established as shown in Fig. 2. In the NOESY experiment, the cross-peaks of H-2/Me-9 and H-2/H-3*β* indicated that those groups were *β*-oriented. Thus, the acetyl group at C-2 was assigned as being *α*-oriented. The orientation of H-5*α* was confirmed from the NOESY correlation between H-3*α* and H-5. Hence, the acetyl group at C-5 was assigned as being *β*-oriented (Fig. 2). Accordingly, compound **1**, with a negative specific optical rotation, was identified as (−)-5-exo-acefoxybornyl acetate. This compound has been synthesized previously, but this is the first report of this compound from a natural source (Allen et al., 2011).

Compound **2** possessed a molecular formula of $C_{12}H_{20}O_3$ based on HR-ESI-MS (*m/z* 235.1302 [M + Na] +, calcd for $C_{12}H_{20}O_3Na$ 235.1305) analysis. Compound **2** was identified as (1*S*,2*R*,4*S*,5*S*)-5-hydroxy-1,7,7-trimethylbicyclo [2.2.1]heptan-2-yl acetate by comparing its NMR data with those of the synthesized compound (Acerson et al., 2015).

(−)-5-Exo-acefoxybornyl acetate (**1**), light yellow oil, $[\alpha]_D^{20}$ – 40 (*c* = 1, CH_3OH), IR (KBr) ν_{max} 1735, 1558, 1540, 1547, 1364, 1243, and 1032 cm^{-1}, for ^{1}H NMR and ^{13}C NMR data, see Table S1 in Supporting Information; positive ESIMS [M + Na] + *m/z* 277; HR-ESI-MS [M + Na] + *m/z* 277.1407 (calcd for $C_{14}H_{22}O_4Na$ 277.1410).

(1*S*,2*R*,4*S*,5*S*)-5-Hydroxy-1,7,7-trimethylbicyclo [2.2.1]heptan-2-yl acetate (**2**), light yellow oil, $[\alpha]_D^{20}$ – 37 (*c* = 1, CH_3OH); IR (KBr) ν_{max} 2956, 1733, 1456, 1363, 1249, 1126, and 1039 cm^{-1}; for ^{1}H NMR and ^{13}C NMR data, see Table S1 in Supporting Information; positive ESIMS [M + Na] + *m/z* 235; HR-ESI-MS [M + Na] + *m/z* 235.1302 (calcd for $C_{12}H_{20}O_3Na$ 235.1305).

4. Chemotaxonomic significance

In this study, twenty-one compounds, including two new natural products (**1** and **2**), two monoterpenes (**3** and **4**), four sesquiterpenes (**5–8**), two iridoids (**9** and **10**), four steroids (**11–14**), five phenolic compounds (**15–19**), and two alkaloids (**20–21**), were isolated from *V. officinalis*. Among them, eight compounds (**1**, **2**, **6–8**, **13**, **18**, and **21**) are being reported from the family Valerianaceae for the first time, and compounds **9–12** have been obtained from *V. officinalis* for the first time. Detailed chemical review has been carried out on isolated terpenes, valepotriates, and steroids previously isolated from members of the genus *Valeriana* (Table S2 in Supporting Information).

Terpenes (monoterpenes and sesquiterpenes) are widely distributed in the genus *Valeriana* (Patocka and Jakl, 2009; Wang et al., 2010) and can be regarded as the characteristic principal bioactive substances for this genus. Among the isolated terpenes, compounds **3–5** have been reported from the genus *Valeriana*, including *V. officinalis* (Asadollahi-Baboli, 2015; Wang et al., 2015; **3**, **4**, and **5**), *Valeriana sisymbriifolia* Vahl. (Javidnia et al., 2006; **3** and **4**), *Valeriana amurensis* Smir. ex Kom. (Li et al., 2015; Wu et al., 2014; **3**, **4**, and **5**), and *Valeriana fauriei* Briq. (Guo et al., 2006; Lee et al., 1996; **3**, **4**, and **5**). This indicated the chemotaxonomic relationship between *V. officinalis* and other species of *Valeriana*. In addition, two acyclic sesquiterpenes (**6** and **7**) along with a caryophyllene derivative (**8**) were reported from the family Valerianaceae for the first time. Compound **6** was previously obtained from the families, Labiatae (Lai et al., 2013), Compositae (Blanc et al., 2006), Cupressaceae (Lesueur et al., 2006), and Solanaceae (Stoessl and Stothers, 1986); compound **7** has only been obtained from Compositae (Hegazy et al., 2014); and compound **8** has only been isolated from Malvaceae (Williams et al., 1997) and Compositae (Weyerstahl et al., 1997). These data provide new information on the chemical characteristics of Valerianaceae and could be important in helping to differentiate *V. officinalis* from other species of *Valeriana*. Furthermore, valepotriates, characteristic iridoids, are commonly found in *Valeriana* species (Salles et al., 2000). Rupesin B (**9**) has only been reported from *Valeriana jatamansi* Jones (Wang et al., 2014) and *Patrinia rupestris* (Yang et al., 2006), and jatamanvaltrate P (**10**) has only been isolated from *V. jatamansi* (Wang et al., 2014). All the abovementioned species belong to the family Valerianaceae, which verified that these genera might share similar biosynthesis pathways for their metabolites.

Four steroids (**11–14**) and five phenolic compounds (**15–19**) were purified in the present study. Although β-sitosterol (**14**) is widely distributed in many plant species, the α, β-unsaturated ketone derivatives of β-sitosterol (**11–13**) are rarely reported from the plants of *Valeriana* (Wang et al., 2010). Compound **11** was observed in *Valeriana polystachya* Smith (De Ávila et al., 2018) and *V. jatamansi* (Tian et al., 2012), and compound **12** was reported in *V. polystachya* (De Ávila et al., 2018). Moreover, this is the first report of 7-oxo-*β*-sitosterol (**13**) from the family Valerianaceae. The abovementioned data not only imply a close relationship between *V. officinalis* and the other two species but also indicate that the α, β-unsaturated ketone derivatives of β-sitosterol (**11–13**) could be chemotaxonomic markers for *Valeriana*. In addition, the three obtained phenolic compounds, benzoic acid (**15**), *trans*-cinnamic acid (**16**), and phthalate (**17**), are common chemical components of many plant species; thus, they have little taxonomic value. This is the first report of 2-methoxy-4-(3-methoxy-l-propenyl)-phenol (**18**) from the family Valerianaceae, and it could serve as chemotaxonomic marker for distinguishing *V. officinalis*.

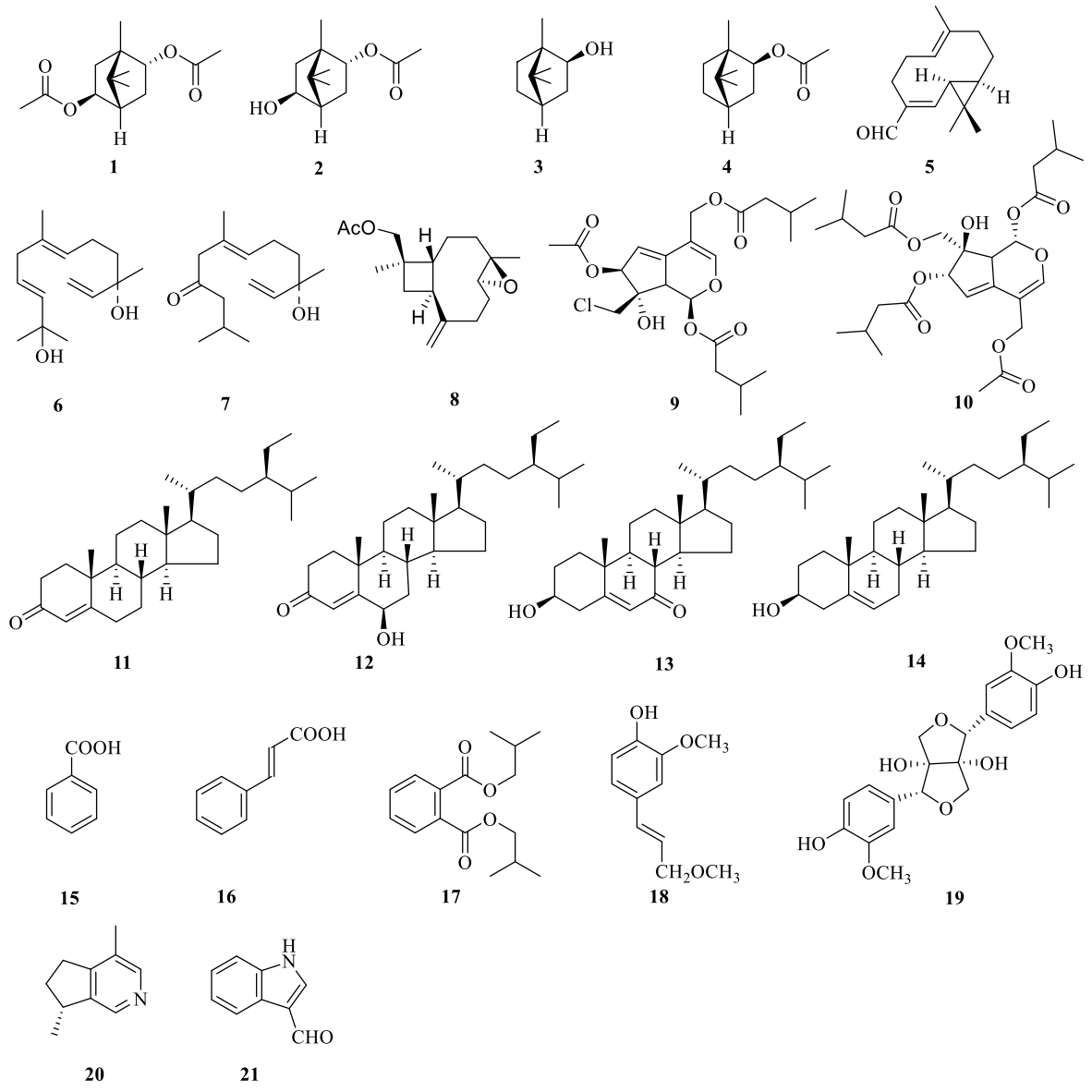

Fig. 1. Chemical structures of **1–21**.

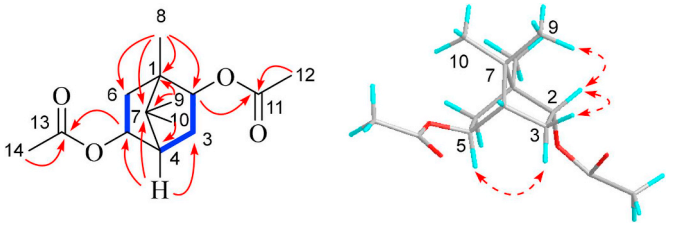

Fig. 2. Key HMBC(→) and $^{1}H–^{1}H$ COSY (—) correlations of **1** and key NOESY (⇢) correlations of **1**.

Few alkaloids have been reported from the genus *Valeriana* (Patocka and Jakl, 2009; Wang et al., 2010). (−)-Actinidine (**20**) has only been reported from *V. officinalis* (Buckova et al., 1977; Janot et al., 1979; Torssell and Wahlberg, 1966). Thus, (−)-actinidine could be considered as an important chemotaxonomic marker for the *V. officinalis* and *Valeriana* genus. Indole-3-carbaldehyde (**21**) is widely distributed in terrestrial plants. However, this is the first report of this compound from the family Valerianaceae, and it could be used as a potential chemotaxonomic marker.

In conclusion, the identified compounds (**1**, **2**, **6–13**, **18**, and **21**) provide several potential chemotaxonomic markers for *V. officinalis*. This study enriches the chemical diversity of the genus *Valeriana* and provides new chemotaxonomic markers for *V. officinalis* and the genus *Valeriana*.

CRediT authorship contribution statement

Shuliang Wang: Writing - original draft. **Yanrong Zeng:** Validation. **Yanan Li:** Data curation. **Li He:** Resources. **Zhanxing Hu:** Data curation, Formal analysis. **Liejun Huang:** Data curation, Formal analysis. **Wei Gu:** Data curation, Formal analysis. **Chunmao Yuan:** Writing - review & editing. **Xiaojiang Hao:** Writing - review & editing.

Declaration of competing interest

The authors have declared that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bse.2020.104041.

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