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Antioxidant and anti-inflammatory activity of constituents isolated from *Dendrobium nobile* (Lindl.)

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Dendrobium nobile (Lindl.) have long been used as herbal tea and a traditional herbal medicine to treat Alzheimer's disease (AD). In the current study, nineteen compounds (**1–19**), including two new vitamin E homologues (**1–2**), one new sesquiterpene (**6**), and two new dendrobines (**7, 8**), were isolated and identified from stems of *Dendrobium nobile*. Their structures were elucidated on the basis of NMR, ¹³C NMR calculation, and DP4⁺ probability analyses. The absolute configurations of new compounds were determined by electronic circular dichroism (ECD) data analysis. Antioxidant, anti-inflammatory, and cytotoxic activities of isolated compounds were evaluated. Among them, compound **2** demonstrated significant antioxidant activity compared with ascorbic acid (VC), while compounds **2** and **4** also exhibited an equal effect to positive control cisplatin. This study on the biological activity of the new vitamin E homologues from *Dendrobium nobile* may indicate its potential application in the pharmaceutical and food industries.

KEYWORDS

Dendrobium nobile Lindl., chemical constituents, antioxidant, anti-inflammatory activities, structure-activity relationship

Introduction

Dendrobium plants (Orchidaceae) are mainly distributed throughout Asia and the Pacific islands. There are 81 species of *Dendrobium* in China, mostly distributed in the South of the Tsinling Mountains of China (Zheng et al., 2018; Wang, 2021a). Owing to their well-known nutritional value and medicinal properties, the genus *Dendrobium* (Orchidaceae) have attracted interest in many health products and pharmaceutical fields (Teixeira da Silva and Ng, 2017). The species *Dendrobium nobile* Lindl, an edible, ornamental, and also a medicinal plant, is one of the four well-known plant sources

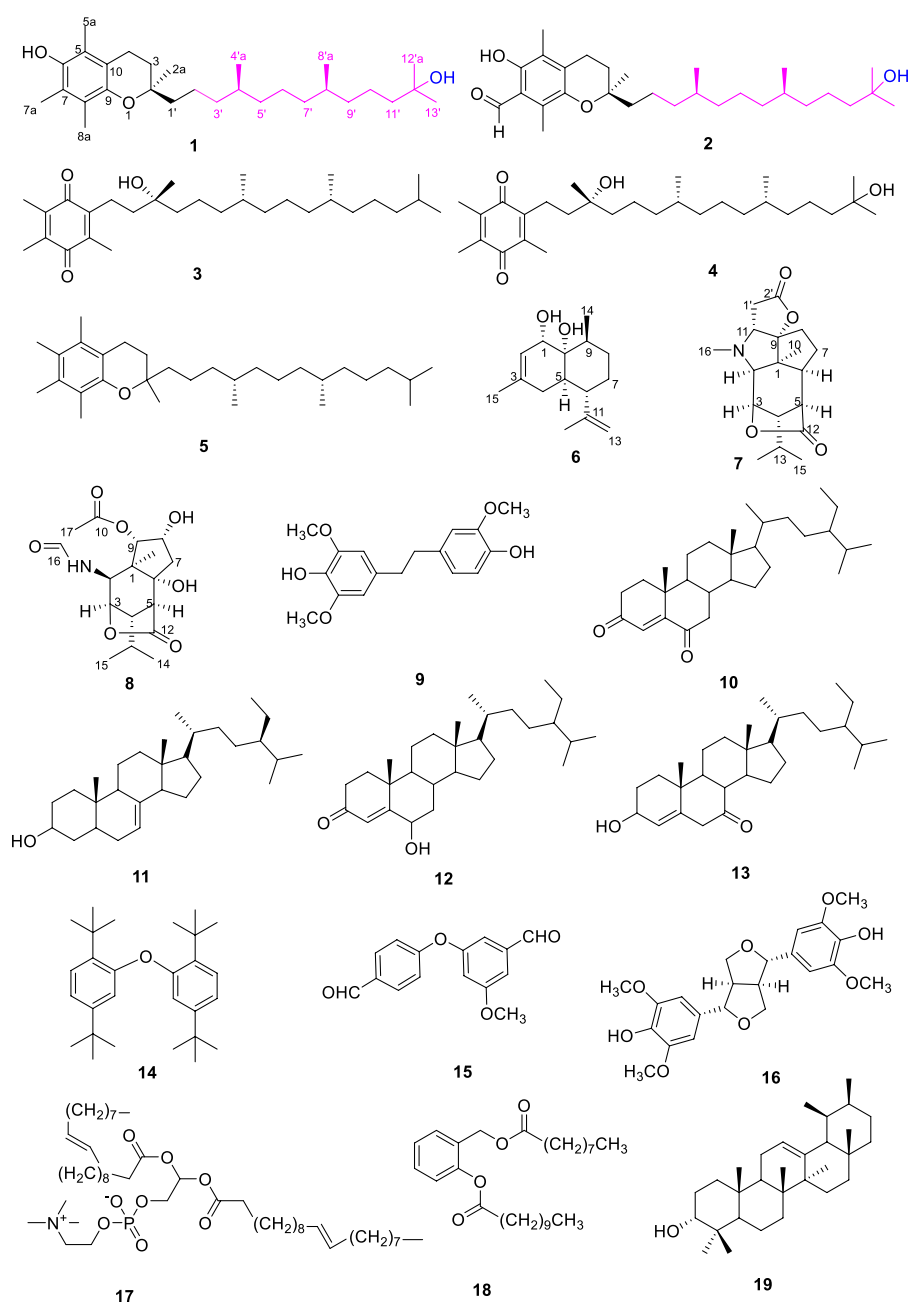


FIGURE 1
Structures of compounds 1–19.

of “Shi Hu”, mainly distributed in southwest China, as Sichuan, Guizhou, and Yunnan (Wang, 2021b). Abundant bioactive constituents of this plant have been previously obtained, including sesquiterpenes (Ling et al., 2021), phenanthrene, bibenzyl derivatives (Cheng et al., 2020), glucosides (Zhao et al., 2001), and alkaloids (Liu and Zhao, 2003). In order to further reveal and utilize the potential value of *Dendrobium nobile* as an industrial crop used in the pharmaceutical and

food industries, we conducted the current study. As a result, nineteen compounds (1–19) (Figure 1), including two new vitamin E homologues (1–2), one new sesquiterpene (6), and two new dendrobines (7, 8), were isolated and identified from the stems of *D. nobile*. In addition, the antioxidant, anti-inflammatory, and anti-tumour activities of the compounds (1–19) were evaluated. These outstanding properties of *Dendrobium nobile* will better expand its applications in

antioxidant, anti-inflammatory, and anti-tumour activities area, especially in the field of pharmaceuticals and food industries.

Materials and methods

General experimental procedures

Optical rotations were measured on an AntonPaar MCP500 polarimeter. IR spectra were performed on a Shimadzu IR spectrometer with KBr disk. HRESIMS were used for a Bruker maXis TOF-Q mass spectrometer. Bruker DRX-500 spectrometer was used to measure the NMR spectra. The UV spectra were recorded on a Shimadzu UV-2600 PC spectrometer. Silica gel (100–200 mesh, 200–300 mesh, Qingdao, China), YMC*GEL ODS-A (S-50 μm , 12 nm) (YMC Co., Ltd., Kyoto, Japan), Sephadex LH-20 (GE, Sweden) were used for column chromatography. Semipreparative HPLC was used for ODS column (YMC-ODS-A). CD spectra were performed on a Biologic MOS-450 spectra polarimeter.

Plant material

The stems of *Dendrobium nobile* were provided by the Chengming Shihu Industrial Development in October, 2020. The sample was botanically identified by Prof. Dan Zhang. A voucher specimen (No. GFM20201024) has been deposited at the Processing and Preparation Laboratory of Traditional Chinese Medicine, Southwest Medical University (Luzhou, China).

Extraction and isolation

The air-dried stems (2 kg) of *Dendrobium nobile* were crushed and extracted with 95% EtOH (4 \times 20 L, 3 days each). After the solvent was evaporated under reduced pressure. The extract (172.6 g) was subjected to column chromatography (CC) over MCI resin and eluted with EtOH-H₂O (50, 70, 90 and 100%, v/v), to obtain four fractions (Fr.1- Fr.4).

Fr. 1 (62.6 g) was subjected to silica gel column chromatography with gradient elution using methylene chloride/methanol (40:1 to 0:1, v/v) to give eleven subfractions (Fr. 1-1 and Fr.1-11). Fr. 1-2 (1.9 g) was separated by silica gel column with petroleum ether/ethyl acetate (from 15:1 to 0:1, v/v) to yield Fr.1-2-1~Fr.1-2-10. Fr.1-2-2 was analyzed by TLC, and the preparation condition was dichloromethane: acetone = 40:1 to obtain compound **16** (6.9 mg). Compound **17** (tR = 25 min, 47.3 mg) and compound **18** (tR = 32 min, 13.7 mg) were purified from Fr.1-2-3, using HPLC (MeOH/H₂O, 55:45, v/v). Fr.1-2-4 was isolated by HPLC (MeOH/H₂O, 55:45, v/v) to obtain compound **19** (tR = 45 min, 23.7 mg).

TABLE 1 ¹H and ¹³C NMR (600 MHz) data for **1** and **2** in CDCl₃.

| No. | 1 | | 2 | |
|---------|----------------------------|-------------------------------|----------------------------|-------------------------------|
| | δ_{C} , type | δ_{H} (J in Hz) | δ_{C} , type | δ_{H} (J in Hz) |
| 1 | — | — | — | — |
| 2 | 74.5, C | — | 75.2, C | — |
| 3 | 31.6, CH ₂ | 1.78, m | 30.8, CH ₂ | 1.82, m |
| 4 | 20.8, CH ₂ | 2.60, t (6.9) | 18.4, CH ₂ | 3.03, t (6.8) |
| 5 | 118.6, C | — | 124.2, C | — |
| 6 | 144.5, C | — | 155.8, C | — |
| 7 | 121.1, C | — | 114.5, C | — |
| 8 | 122.6, C | — | 138.4, C | — |
| 9 | 145.5, C | — | 144.0, C | — |
| 10 | 117.4, C | — | 117.6, C | — |
| 1' | 39.7, CH ₂ | 1.53, m | 39.5, CH ₂ | 1.55, m |
| 2' | 21.0, CH ₂ | 1.39, m | 20.9, CH ₂ | 1.40, m |
| 3' | 37.6, CH ₂ | 1.27, m | 37.6, CH ₂ | 1.26, m |
| 4' | 32.8, CH | 1.39, m | 32.8, CH | 1.39, m |
| 5' | 37.5, CH ₂ | 1.27, m | 37.4, CH ₂ | 1.26, m |
| 6' | 24.5, CH ₂ | 1.06, m | 24.5, CH ₂ | 1.06, m |
| 7' | 37.4, CH ₂ | 1.07, m | 37.4, CH ₂ | 1.08, m |
| 8' | 32.7, CH | 1.39, m | 32.7, CH | 1.39, m |
| 9' | 37.4, CH ₂ | 1.07, m | 37.4, CH ₂ | 1.08, m |
| 10' | 21.8, CH ₂ | 1.30, m | 21.8, CH ₂ | 1.30, m |
| 11' | 44.3, CH ₂ | 1.43, m | 44.3, CH ₂ | 1.43, m |
| 12' | 71.2, C | — | 71.1, C | — |
| 13' | 29.3, CH ₃ | 1.25, m | 29.7, CH ₃ | 1.25, m |
| Me-2a | 23.8, CH ₃ | 1.23, m | 23.7, CH ₃ | 1.23, s |
| Me-5a | 11.3, CH ₃ | 2.11, s | 11.3, CH ₃ | 2.15, s |
| Me-7a | 12.3, CH ₃ | 2.16, s | 194.0, C | 10.20, s |
| Me-8a | 11.8, CH ₃ | 2.14, s | 13.2, CH ₃ | 2.17, s |
| Me-4'a | 19.7, CH ₃ | 0.85, d (6.6) | 19.7, CH ₃ | 0.85, d (6.6) |
| Me-8'a | 19.7, CH ₃ | 0.86, d (6.6) | 19.7, CH ₃ | 0.86, d (6.3) |
| Me-12'a | 29.2, CH ₃ | 1.18, m | 29.3, CH ₃ | 1.26, m |

Fr. 2 (6.2 g) was isolated into five subfractions (Fr. 2-1 and Fr.2-5) through silica gel column chromatography with gradient elution using petroleum ether/ethyl acetate (30:1 to 0:1, v/v). Compound **15** (5.9 mg) was purified from Fr. 2-3, and the preparation condition was dichloromethane: acetone (40:1).

Fr. 3 (29.7 g) was separated by silica gel column chromatography with gradient elution using petroleum ether/ethyl acetate (30:1 to 0:1, v/v) to produce nine subfractions (Fr. 3-1 and Fr.3-9). Fr. 3-1 was analyzed by TLC, and further purified by preparative TLC with dichloromethane/acetone (40:1) to afford compounds **3** (6.2 mg) and **4** (7.1 mg). Fr. 3-2 (599 mg) was fractionated into four subfractions (Fr. 3-2-1 and Fr.3-2-4) by silica gel column chromatography with gradient elution using petroleum ether/ethyl acetate (15:1 to 0:1, v/v). Fr. 3-2-4 was separated by Sephadex LH-20 column and purified by PTLC

TABLE 2 ^1H and ^{13}C NMR (600 MHz) data for 6-8 in CDCl_3 .

| NO. | 6 | | 7 | | 8 | |
|-----|----------------------------|-------------------------------|----------------------------|-------------------------------|----------------------------|-------------------------------|
| | δ_{C} , type | δ_{H} (J in Hz) | δ_{C} , type | δ_{H} (J in Hz) | δ_{C} , type | δ_{H} (J in Hz) |
| 1 | 68.9, CH | 4.13, d (4.8) | 54.5, C | — | 49.4, C | — |
| 2 | 122.0, CH | 5.38, d (6.0) | 68.7, CH | 2.90, s | 50.5, CH | 4.49, d (10.3) |
| 3 | 128.7, C | — | 79.1, CH | 4.93, m | 82.1, CH | 4.44, d (4.5) |
| 4 | 37.4, CH_2 | 2.59, m, 1.96, m | 51.2, CH | 2.17, m | 53.0, CH | 2.18, m |
| 5 | 46.8, CH | 1.93, m | 43.5, CH | 2.25, m, 2.19, m | 48.1, CH | 3.01, d (4.3) |
| 6 | 49.7, CH | 2.47, dd (12.0, 3.6) | 43.7, CH | 2.51, m, 2.44, m | 77.6, C | — |
| 7 | 32.2, CH_2 | 1.45, m | 36.0, CH_2 | 2.20, m, 1.90, m | 56.2, CH_2 | 3.58, m |
| 8 | 32.0, CH_2 | 1.71, m | 30.4, CH_2 | 2.34, m | 64.0, CH | 3.71, m |
| 9 | 42.6, CH | 1.75, m | 104.8, C | — | 79.3, CH | 4.85, s |
| 10 | 72.0, C | — | 25.7, CH_3 | 1.35, s | 170.1, C | — |
| 11 | 148.4, C | — | 69.5, CH | 3.57, d (6.0) | 24.9, CH_3 | 1.29, s |
| 12 | 19.1, CH_3 | 1.71, s | 178.8, C | — | 174.8, C | — |
| 13 | 111.0, CH_2 | 4.75, d (12.0) | 24.9, CH | 1.81, m | 26.6, CH | 2.20, m |
| 14 | 15.2, CH_3 | 1.12, d (6.5) | 20.5, CH_3 | 0.99, s | 21.8, CH_3 | 1.08, d (5.6) |
| 15 | 23.8, CH_3 | 1.72, s | 21.2, CH_3 | 0.98, s | 20.5, CH_3 | 1.01, d (6.0) |
| 16 | — | — | 35.6, CH_3 | 2.57, m | 161.3, CH | 8.25, s |
| 17 | — | — | — | — | 21.4, CH_3 | 2.24, s |
| 1' | — | — | 33.4, CH_2 | 2.43, s | — | — |
| 2' | — | — | 175.9, C | — | — | — |

with petroleum ether/ethyl acetate (3:1) to obtain compounds **5** (9.3 mg) and **6** (5.9 mg). Fr. 3–5 (1.7035 g) was eluted with silica gel column chromatography using petroleum ether/ethyl acetate (10:1 to 0:1, v/v) and was further separated by PTLC and Sephadex LH-20 (MeOH) to obtain compounds **8** (15.2 mg), **9** (6.4 mg), and **10** (3.6 mg). Fr. 3-5-4 was successively subjected to silica gel CC (dichloromethane/acetone, 40:1) and PTLC to get compounds **11** (5.6 mg) and **7** (18.9 mg). Fr.3-7 was prepared by both silica gel column chromatography and PTLC to obtain compound **12** (9.3 mg). Fr.3-8 was prepared by silica gel column chromatography and PTLC to obtain compound **13** (12.8 mg). Fr.3-9 was prepared by silica gel column chromatography and PTLC to obtain compound **14** (5.4 mg).

Fr. 4 (16.3 g) was chromatographed using silica gel CC and eluted by petroleum ether/ethyl acetate (30:1 to 0:1, v/v) to provide six subfractions (Fr. 4-1 and Fr.4–6). Fr. 4-3 was further fractionated through Sephadex LH-20 (MeOH) as well as PTLC (dichloromethane/acetone, 40:1) to obtain compounds **1** (5.1 mg) and **2** (4.0 mg).

12'-hydroxy- α -tocopherol (**1**)

Yellow oil; $[\alpha]_{\text{D}}^{25}$ -2.1 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 290 (2.64) nm; IR (film) ν_{max} 3430, 2970, 1760, 1450, 1360, 1218, 1190, 1118, 1080, 990, cm^{-1} ; ^1H NMR and ^{13}C NMR data, see Table 1; HRESIMS m/z 445.3638 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{29}\text{H}_{49}\text{O}_3$, 445.3690).

Aldehyde- α -tocopherol (**2**)

Yellow oil; $[\alpha]_{\text{D}}^{25}$ -1.4 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 297 (4.32) nm; IR (film) ν_{max} 3409, 2960, 1745, 173, 1650, 1558, 1460, 1380, 1260, 1060, 940 cm^{-1} ; ^1H NMR and ^{13}C NMR data, see Table 1; HRESIMS m/z 459.3425 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{29}\text{H}_{47}\text{O}_4$, 459.3483).

Hydroxy-(+)-epicubenol (**6**)

White amorphous solid; $[\alpha]_{\text{D}}^{25}$ +42 (c 0.2, MeOH); IR (film) ν_{max} 3340, 2968, 2896, 1460, 1381, 1058, 1012, 896 cm^{-1} ; ^1H NMR and ^{13}C NMR data, see Table 2; HRESIMS m/z 219.1745 $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ (calcd for $\text{C}_{15}\text{H}_{23}\text{O}$, 219.1702).

Dendroterpene F (**7**)

White solid; $[\alpha]_{\text{D}}^{25}$ -15.9 (c 0.1, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 230 (3.15), IR (film) ν_{max} 3440, 2950, 2862, 1780, 1590, 1460, 1383, 1240, 1040 cm^{-1} ; ^1H NMR and ^{13}C NMR data, see Table 2; HRESIMS m/z 320.1941 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_4$, 320.1947).

Dendroterpene G (**8**)

White solid; $[\alpha]_{\text{D}}^{25}$ +12.4 (c 0.20, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 219 (3.45), IR (film) ν_{max} 3420, 2980, 1780, 1678, 1505, 1380, 1243, 1024 cm^{-1} ; ^1H NMR and ^{13}C NMR data, see Table 2; HRESIMS m/z 354.1565 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_7$, 354.1601).

ECD calculations

The calculations of compounds (1–2, 7–8) were achieved using Gaussian 16. At the B3LYP/6–311+G (d,p) level, ECD calculations were chosen for the optimized conformations. And finally, the ECD spectra were obtained by SpecDis version 1.63 software.

Antioxidant activity assays

The DPPH radical scavenging activity was performed according to a previously described method.³⁰ Briefly, a series of various concentrations of the samples (200, 100, 50, 25 μ M) were mixed with DPPH (0.2 mM) in a 96-well microplate. After that, the absorbance of the mixture to react was measured at 517 nm. Percentages of the free radical-scavenging capacity of all the compounds (1–19) were calculated with the following equation:

$$\text{Scavenging rate (\%)} = (A_0 - A_1)/A \times 100 \quad (1)$$

A_0 and A_1 respectively represent the absorbance of the control and the samples. The ascorbic acid was the positive control in this assay. All the results were the averages of triplicate measurements. The IC_{50} values were calculated by Graphpad prism 7.0 statistic software.

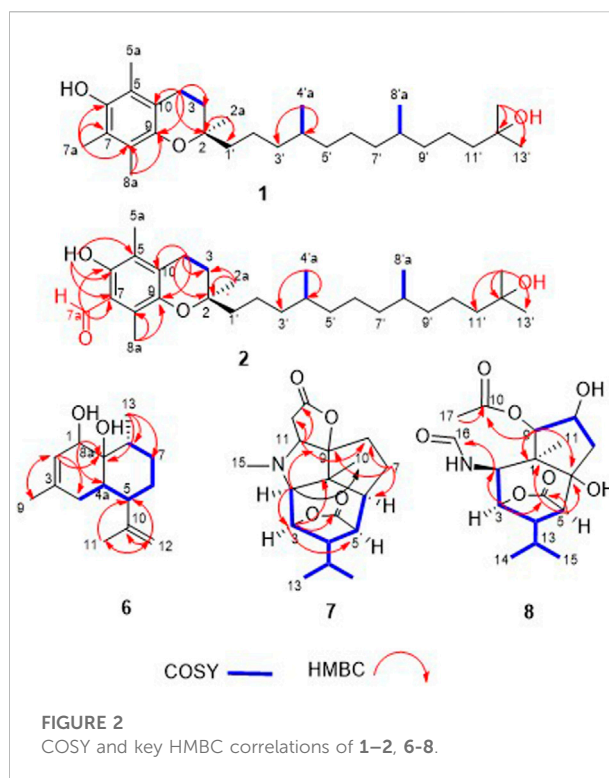
Inhibition of NO production assays

The RAW 264.7, Hela, and HepG2 cells were obtained from Southwest Medical University, and cultured in DMEM medium with 10% FBS, 2 mM glutamine, 100 U/mL of penicillin, and 100 μ g/mL of streptomycin at 37°C under 5% CO₂ atmosphere. The cytotoxicities of compounds (1–19) against the cell lines including RAW 264.7, Hela, and HepG2 cells were determined by the MTT method as previously reported (Lei et al., 2021). The RAW 264.7 cells were plated in six-well plates with 1×10^6 cell/well. After 24 h, the cells were pretreated with compounds 1–19 (33 μ M) for 2 h. The Griess method was used to detect NO production as previously described.

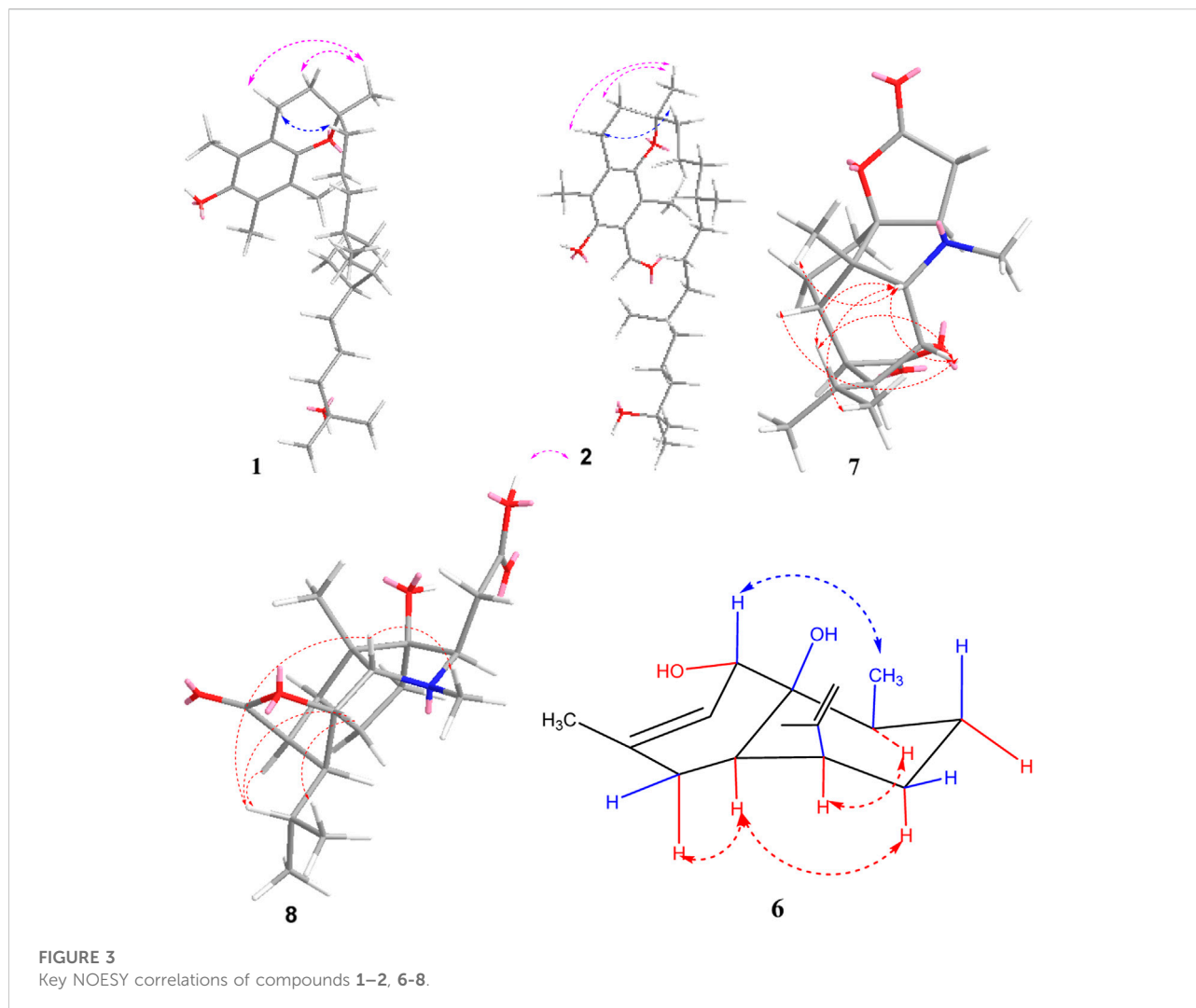
Results and discussion

Identification of compounds

Compound 1 was obtained as a yellow oil. Its molecular formula was assigned as C₂₉H₅₀O₃ by the HRESIMS at m/z 445.3638 [M–H][–]. The ¹H NMR data (see Supplementary Figure S2 in Supplementary Material) of compound 1 revealed the presence of eight methyl signals at 0.85 (d, $J = 6.6$ Hz, Me-



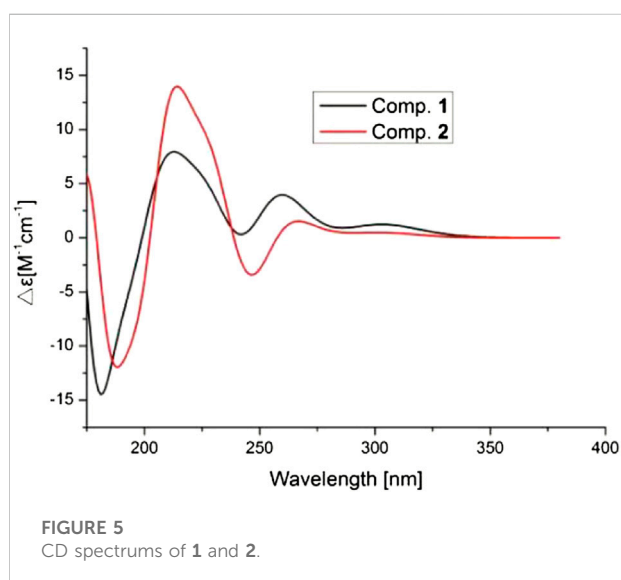
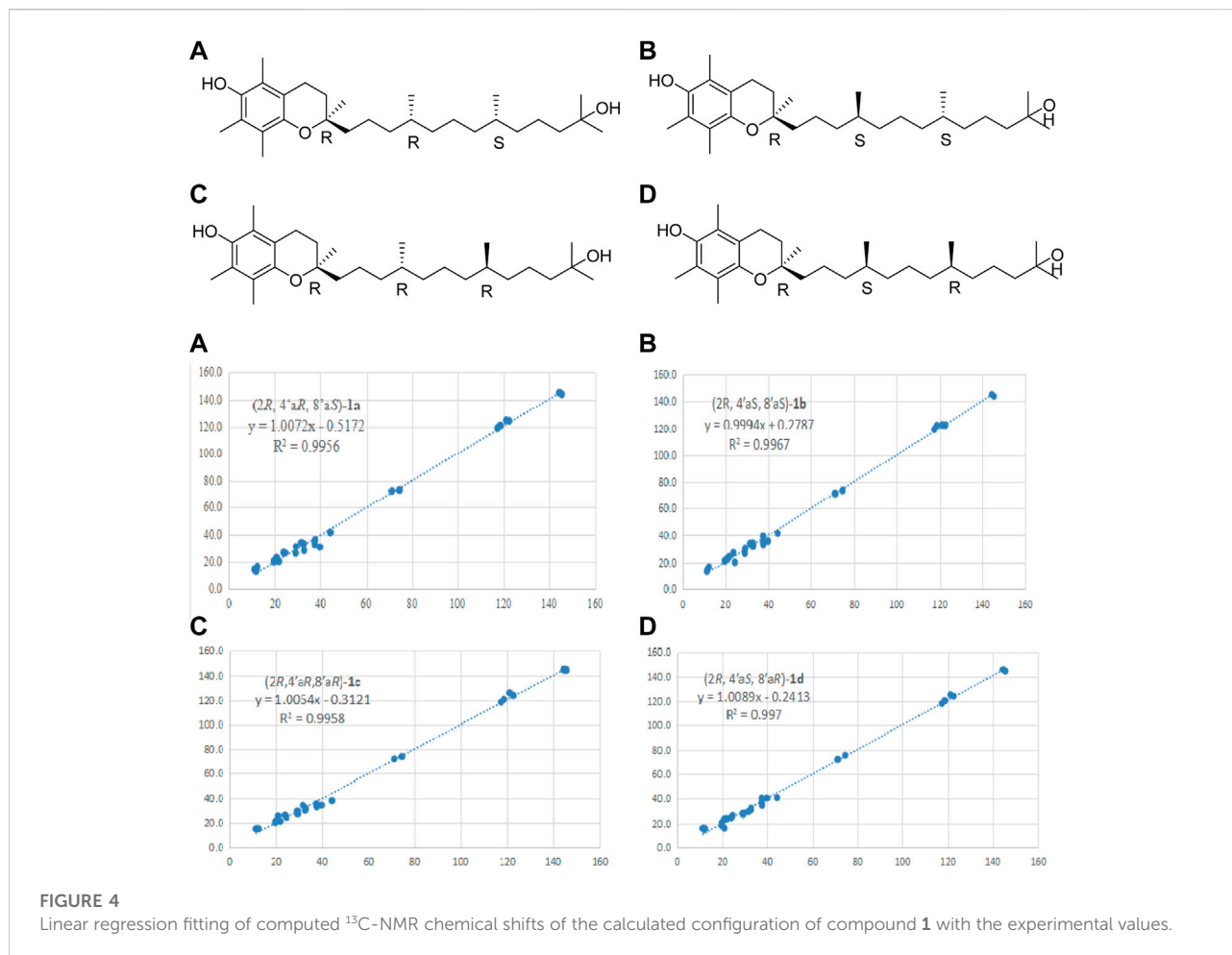
4'a), 0.86 (d, $J = 6.3$ Hz, Me-8'a), 1.18 (m, Me-7a), 1.18 (m, Me-12'a), 1.25 (m, Me-13'), 1.23 (m, Me-2a), 2.11 (s, Me-5a), 2.16 (s, Me-7a), 2.14 (s, Me-8a), two methylenes at δ_H 2.60 (t, $J = 6.9$ Hz, H-4), 1.78 (m, H-3), and other overlapped protons (Table 1). Meanwhile, the ¹³C NMR data (see Supplementary Figure S3 in Supplementary Material) showed 29 carbon signals corresponding to eight methyls, eleven methylenes, two methines carbons, and four oxygenated carbons, including two olefinic carbon, and four quaternary carbons. The similarity of NMR features of compound 1 with α -tocopherol suggested it was a vitamin E derivative (Fiorentino et al., 2009), with the only difference being the presence of the additional oxygenated carbons at C-12' (δ_C 71.2), which was supported by the HMBC (see Supplementary Figure S5 in Supplementary Material) correlation from H-13' (δ_H 1.25) to C-12'a (δ_C 29.2), C-11' (δ_C 44.3), and C-12' (δ_C 71.2). Furthermore, HMBC correlations between H-4 (δ_H 2.60) and C-3 (δ_C 31.6), C-2 (δ_C 74.5), C-9 (δ_C 145.5), and C-10 (δ_C 117.4) and between H-2a (δ_H 1.23) and C-1' (δ_C 39.7), C-2 (δ_C 74.5), and C-3 (δ_C 31.6) reconfirmed that the side chain located at C-2 (Figure 2). In addition, the relative stereochemistry of compound 1 was deduced based on NMR data and NOESY experiment (see Supplementary Figure S7 in Supplementary Material). The configuration of C-2, C-4'a, and C-8'a at the side chain of compound 1 was determined by comparing the ¹³C NMR data with the related compound, α -tocopherol and α -tococomonoenol (Fiorentino et al., 2009) (Kyeong-Hwa et al.,



2013). The observed NOESY correlations from H-3/H-2a to H-4 α (they were in the same plane), from H-1' β to H-4 β , demonstrated that the chirality (C-2) of the compound **1** was *R* (Figure 3). In order to confirm the configuration of **1**, the calculated NMR chemical shifts of four possible diastereomers, (2*R*, 4'*aR*, 8'*aS*)-**1a**, (2*R*, 4'*aS*, 8'*aS*)-**1b**, (2*R*, 4'*aR*, 8'*aR*)-**1c**, and (2*R*, 4'*aS*, 8'*aR*)-**1d**, were obtained by DP4⁺ probability analysis at the PCM/mPW1PW91/6-31+G (d,p) level (see Supplementary Figure S42 in Supplementary Material). As shown in Figure 4, DP4⁺ analysis suggested that (2*R*, 4'*aS*, 8'*aR*)-**1d** was the most likely candidate with 98.26% probability. Meanwhile, the CD spectrum of compound **1** showed a negative Cotton effect at 183 nm and a positive Cotton effect at 208 nm suggesting the 2*R*, 4'*aS*, and 8'*aR* configuration in compound **1** (Figure 5). Hence compound **1** was determined and named 12'-Hydroxy- α -tocopherol.

Compound **2** was obtained as a yellow oil, of which the molecular formula was assigned to be C₂₉H₄₈O₄ by ¹³C NMR

data and HRESIMS *m/z* 459.3425 [M-H]⁻. It is found that the ¹H and ¹³C NMR spectroscopic data of compound **2** (Table 1) were similar to those of compound **1**, indicating that compound **2** was also an α -tocopherol derivative, with the major difference being the absence of a methyl signal at C-7, while the presence of one additional aldehyde group (δ_{H} 10.20, δ_{C} 194.0) in compound **2**. This conclusion was confirmed by the HMBC (see Supplementary Figure S12 in Supplementary Material) correlations from H-7a to C-7 (δ_{C} 114.5), C-6 (δ_{C} 155.8), and C-8 (δ_{C} 138.4). On the basis of the similar chemical shifts and the biosynthetic pathway, we suggest that compounds **1** and **2** had the same relative configurations for C-2, C-4'*a*, and C-8'*a*. Furthermore, the observed NOESY (see Supplementary Figure S14 in Supplementary Material) correlations of compound **2** also supported the above deductions (Figure 3). The absolute configurations of compound **2** was determined by comparison of the CD spectrum. As well, the CD spectrum of compound **2** had a similar Cotton effect to those of compound **1** (Figure 5).



Therefore, the structure of compound **2** was determined as 2R, 4'aS, and 8'aR, and named 7-aldehyde- α -tocopherol.

The molecular formula of compound **6** was assigned to be $\text{C}_{15}\text{H}_{24}\text{O}_2$ on the basis of the HRESIMS spectrum at m/z 219.1745 $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ and ^{13}C NMR data. Additionally, a detailed analysis of its ^1H NMR data (Table 2) exhibited the existence of three olefinic protons at δ_{H} 5.38 (1H, s, H-2) and 4.75 (2H, d, $J = 12.0$, H-13), three methyl signals at δ_{H} 1.72 (3H, s, H₃-15), 1.71 (3H, br. s, H₃-12), and 1.12 (3H, d, $J = 6.5$, H-14). The ^{13}C NMR spectrum of compound **6** exhibited 15 carbon signals, which were assigned to three methyl groups, four methylenes, four methines, two quaternary carbons, and two oxygenated carbons. The ^1H and ^{13}C NMR data of compound **6** suggested that it was very similar to a related sesquiterpene, decalin triol (Kawatsura et al., 1997), except for the presence of signals for an additional olefinic proton group (δ_{H} 5.38, δ_{C} 122.0), a methyl group (δ_{H} 1.72, δ_{C} 23.8), and the lack of signals for a hydroxy group. HMBC (see Supplementary Figure S19 in Supplementary

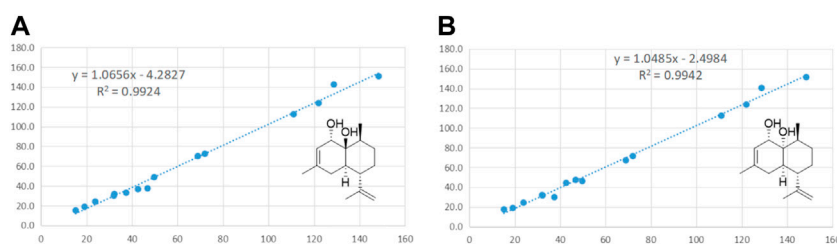


FIGURE 6

Linear regression fitting of computed ^{13}C -NMR chemical shifts of the calculated configuration of compound **6** with the experimental values.

Material) correlations between H-2 (δ_{H} 5.38) and C-15 (δ_{C} 23.8), C-4 (δ_{C} 37.4), and C-10 (δ_{C} 72.0) and between H-15 (δ_{H} 1.72) and C-4 (δ_{C} 37.4), C-2 (δ_{C} 122.0), and C-3 (δ_{C} 128.7) reconfirmed that the methyl group located at C-3. The NOESY (see Supplementary Figure S21 in Supplementary Material) correlations from H-1 to H₃-13 and H-4 α , from H-4 α to H-5, and from H-5 to H-9 indicated that H-1, H₃-14, H-6, and H-4 α were on the same side, while H-5 and H-9 located on the opposite side (Figure 3). To further confirm the configuration of compound **6**, the theoretical NMR calculations and DP4+ probability were performed. The ^{13}C NMR chemical shifts of **6a** and **6b** were calculated at the PCM/mPW1PW91/6-31+G (d,p) level. According to the DP4+ probability analyses, **6b** was the most likely candidate with 99.99% probability. Accordingly, the configuration of **6** was established (Figure 6). Therefore, compound **6** was determined to be 1-hydroxy-(+)-epicubenol.

Compound **7** was obtained as a white amorphous powder. Its molecular formula, $\text{C}_{18}\text{H}_{25}\text{NO}_4$, was established on the HRESIMS (m/z 320.1941 [M+H]⁺). The ^1H NMR spectrum (Table 2) of compound **7** displayed resonances attributed to four methyl groups at δ_{H} 0.98 (3H, s, H₃-15), δ_{H} 0.99 (3H, s, H₃-14), δ_{H} 1.35 (3H, s, H₃-10), and δ_{H} 2.57 (3H, m, H₃-16), as well as an oxymethine groups at 4.93 (m, H-3). The ^{13}C NMR spectrum of compound **7** displayed 18 carbon signals, which were assigned to four methyl groups, three methylenes, seven methines, four

quaternary carbons, including an oxygenated quaternary carbon, two carbonyl, and an quaternary carbon center. The above data suggested that compound **7** was very similar to those of (-)-(1R,2S,3R,4S,5R,6S,9S,11R)-11-carboxymethyldendrobin (Meng et al., 2017), which was an analogue of dendrobin (Wang et al., 1985; Cassayre and Zard, 1999). The major difference was due to the presence of signals of the oxygenated quaternary carbon (δ_{C} 104.8) and the lactone bridge (C2'-C9) in compound **7**, instead of one methine in (-)-(1R,2S,3R,4S,5R,6S,9S,11R)-11-carboxymethyldendrobin, which was supported by the HMBC (see Supplementary Figure S26 in Supplementary Material) correlations from H-2 (δ_{H} 2.90) to C-9 (δ_{C} 104.8), C-3 (δ_{C} 79.1), C-11 (δ_{C} 69.5), C-1 (δ_{C} 54.5), and C-10 (δ_{C} 25.7), from H-7 (δ_{H} 1.90) to C-9 (δ_{C} 104.8), C-1 (δ_{C} 54.5), C-5 (δ_{C} 43.5), and C-8 (δ_{C} 30.4), from H-1' (δ_{H} 2.43) to C-2' (δ_{C} 175.9), C-9 (δ_{C} 104.8), and C-11 (δ_{C} 69.5) (Figure 2). In the NOESY spectrum (see Supplementary Figure S28 in Supplementary Material), the key correlations of H-2 with H₃-14, H-10, and H-13, of H-3 with H-13, H-2, and H-6 suggested that these protons were co-facial. The relative configuration of **7** was determined as 1R,2S,3R,4S,5R,6S,11R. The absolute configuration of the (-)-(1R,2S,3R,4S,5R,6S,9S,11R)-11-carboxymethyldendrobin was determined using CD spectrum and synthetic product (Meng et al., 2017) (Cassayre and Zard, 1999). With

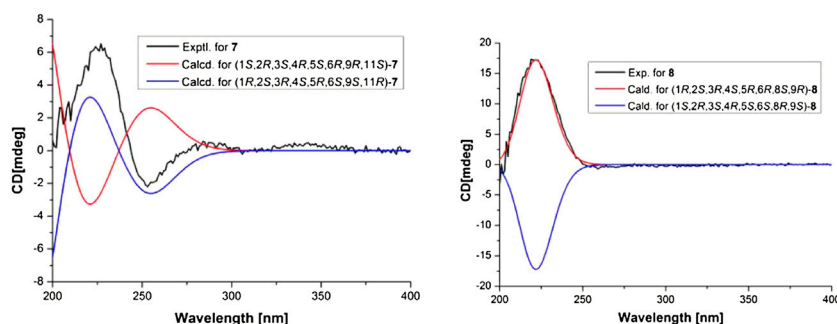
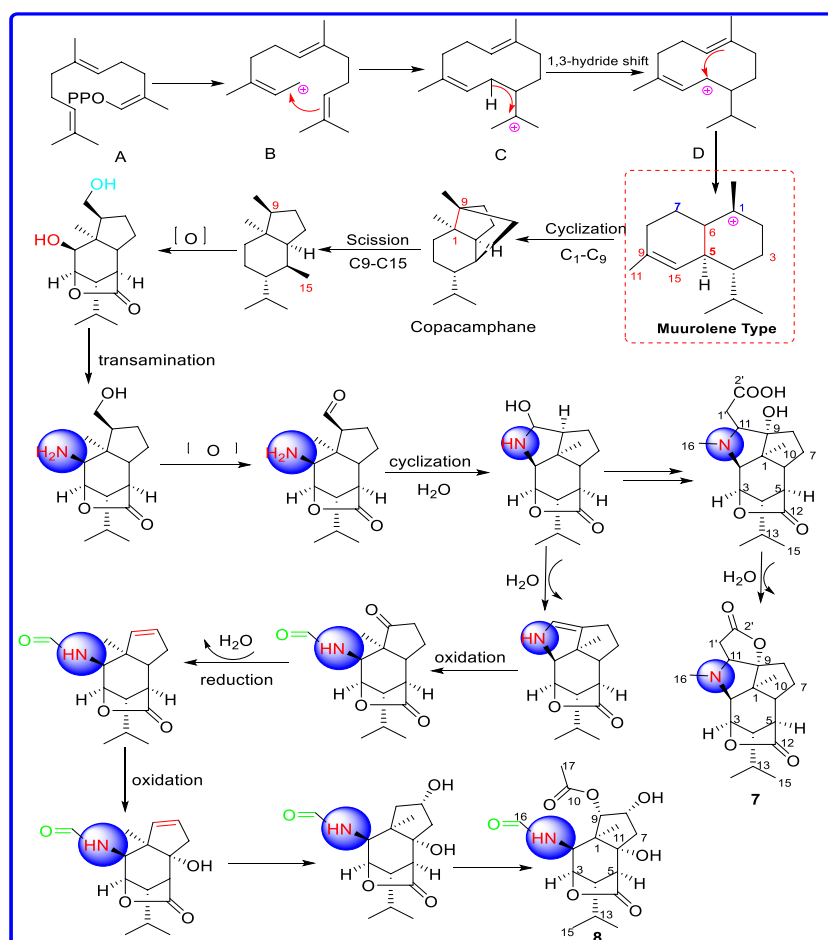


FIGURE 7

Comparison between calculated and experimental ECD spectra of **7** and **8**.



SCHEME 1
Plausible biosynthetic pathway of compounds **7** and **8**.

comparison to the ^{13}C NMR data of both compounds, compound **7** possessed the same relative configuration as the known compound. In order to determine the absolute configurations of **7**, the electronic circular dichroism (ECD) spectrum of **7** was carried out. As a result, the calculated spectrum of $(1R,2S,3R,4S,5R,6S,9S,11R)$ -**7** matched well with the experimental data (Figure 7), indicating absolute configuration of **7**, to be $1R,2S,3R,4S,5R,6S,9S,11R$. Thus, compound **7** was established and named dendroterpene F.

The molecular formula of compound **8** was assigned to be $\text{C}_{17}\text{H}_{25}\text{NO}_6$ on the basis of HRESIMS. And detailed analysis of the NMR data (Table 2) (see Supplementary Figure S32 in Supplementary Material) of compound **8** implied that it was very similar to those of dendroterpene B (Wang et al., 2019). However, the major difference was that one additional ester carbonyl carbon (δ_{C} 170.1) was present while a double bond was absent in compound **8**, indicating that the double bond was reduced to methines. And the key NOESY (see Supplementary

Figure S37 in Supplementary Material) correlations of H-2 with H₃-11, H-13, of H-3 with H₃-15, H-13, and of H-5 with H-13 suggested the relative configuration was $1R, 2S, 3R, 4S, 5R, 6R, 8S, 9R$ (Figure 3). Meanwhile, the similar chemical shifts of compound **8** suggested it had the same configurations for C-1, C-2, C-3, C-4, C-5, and C-11 as dendroterpene B, the absolute configuration of which was determined by single crystal X-ray diffraction. Given that both compound **8** and dendroterpene B were isolated from the congeneric species, the absolute configuration of the former was deduced as $1R, 2S, 3R, 4S, 5R, 6R, 8S, 9R$. Then this assignment was confirmed by the calculated ECD spectrum of $(1R, 2S, 3R, 4S, 5R, 6R, 8S, 9R)$ -**8** (Figure 7). Thus, the structure of compound **8** was finally elucidated and named dendroterpene F.

By comparing NMR data with the previous report, the structures of isolated compounds (**3–5, 9–19**) were identified as: α -tocopherolquinone (**3**) (Yan et al., 2015), 2-(3,15-dihydroxy-3,7,11,15-tetramethylhexadecyl)-3,5,6-trimethyl-2,5-

TABLE 3 DPPH free-radical-scavenging of compounds 1–19^a.

| Sample | DPPH inhibition rate (%) | IC ₅₀ (μmol/L) |
|---------------|--------------------------|---------------------------|
| 1 | 43.21 | — |
| 2 | 90.02 | 59.13 ± 2 |
| 3 | 15.88 | — |
| 4 | 18.82 | — |
| 5 | 4.19 | — |
| 6 | 10.34 | — |
| 7 | 18.62 | — |
| 8 | 8.84 | — |
| 10 | 6.22 | — |
| 11 | 36.17 | — |
| 12 | 2.78 | — |
| 13 | 2.45 | — |
| 17 | 2.45 | — |
| 18 | 2.45 | — |
| 19 | 80.36 | 363.77 ± 3 |
| Ascorbic acid | 90.69 | 101.67 ± 0.2 |

^aCompounds that are not shown in this table did not exhibit activity.

cyclohexadiene-1,4-dione (4) (Yan et al., 2015), dl- α -tocopherol (5) (Ghelf et al., 2019), mascatilin (9) (Majumder and Sen, 1987), stigmast-4-ene-3, 6-dione (10) (Shen et al., 2002), (3 β ,5 α ,20R,24R)-ster-7-en-3-ol (11) (Jaha et al., 1995), stigmast-4-en-6 β -ol-3-one (12) (Niu et al., 2001), 7-keto- β -sitosterol (13) (Yu et al., 2007), 2, 2'-oxybis (1, 4)-di-tert-butylbenze (14) (Cao et al., 2020), 3-(4'-formylphenoxy)-4-methoxybenzaldehy-de (15) (Cao et al., 2020), (+)-syringaresinol (16) (Wang et al., 2009), 1,2-di-O-9Z-octadecenoyl-sn-glycero-3-phosphorylcholine (17) (Kwon et al., 2003), methyl 2-nonanoate-3-undecanoate-cyclohexyl-1,4-diene ester (18) (Li and Xu, 2018), eqi- α -amyrin (19) (Albert and Duilio, 2005).

Plausible biosynthetic pathway of compounds 7 and 8

From a biosynthetic perspective, characterized by a picrotoxane carbon skeleton with polycyclic and seven contiguous stereocenters, dendrobines are derived from the same precursor, copacamphane. First, the copacamphane are presumably derived from farnesyl pyrophosphate (FPP) through 1,3-hydride shift, cyclization, reduction, dehydration, and oxygenation to form the core skeleton. Then copacamphane may be transformed via the break-off of carbon-carbon bonds at C (9)~C (15) to form picrotoxane, followed by subsequent transamination, oxidation, cyclization, and methyltransferase at C (2)~C (9) to produce compound 7, which successively undergoes dehydration, oxidation, acetylation to provide compound 8 (Scheme 1).

TABLE 4 Inhibition of NO production with IC₅₀ values of compounds 17 and 19^a.

| Sample | IC ₅₀ (μmol/L) |
|---------------|---------------------------|
| 17 | 36.70 ± 2 |
| 19 | 19.47 ± 1 |
| Dexamethasone | 17.46 ± 2 |

^aCompounds that are not shown in this table did not exhibit activity.

TABLE 5 Cytotoxic (IC₅₀ in μM) Activities of Compounds 1–4^a.

| Sample | IC ₅₀ (HepG2)/μM | IC ₅₀ (Hela)/μM |
|-----------|-----------------------------|----------------------------|
| 1 | >100 | — |
| 2 | 51.28 ± 3 | 18.71 ± 3 |
| 3 | 19.75 ± 1 | — |
| 4 | 37.06 ± 2 | 19.51 ± 1 |
| Cisplatin | 6.58 ± 3 | 14.93 ± 1 |

^aCompounds that are not shown in this table did not exhibit activity.

Biological activities

Antioxidant activity

DPPH assays are common methods to evaluate the antioxidant capacity of compounds, thus the antioxidant capacity of compounds 1–19 were evaluated by DPPH assays (Table 3). As a result, the DPPH radical scavenging assay showed that compound 2 (IC₅₀ = 59.13 ± 2 μM) had a stronger efficiency than that of the positive control (ascorbic acid, VC) (IC₅₀ = 101.67 ± 0.2 μM), while compound 19 (IC₅₀ = 363.77 ± 3 μM) exhibited potent antioxidant activity as compared with the ascorbic acid.

Inhibition of NO production

To evaluate the activities of the isolated compounds, compounds 1–16 were tested by examining their ability to inhibit NO production in LPS-stimulated RAW 264.7 macrophage cells. The test activities showed that compounds 17 and 19 exhibited inhibition of NO production with IC₅₀ values of (19.47 ± 1 μM) and (36.7 ± 2 μM), respectively (Table 4). In addition, compounds 17 and 19 did not exhibit cytotoxic. Therefore, these two compounds might serve as potential lead drug to develop NO inhibitors.

Cytotoxicity activity

The cytotoxic activities of compounds (1–19) against Hela and HepG2 cells were evaluated by MTT assay (Table 5). However, Only compounds 2 and 4 exhibited cytotoxic effects against Hela cell lines with the IC₅₀ values of with IC₅₀ of

($18.71 \pm 3 \mu\text{M}$) and ($19.51 \pm 1 \mu\text{M}$), which were comparable to positive control cisplatin ($14.93 \pm 1 \mu\text{M}$). In addition, compounds **2**, **3**, and **4** showed inhibitory activity against HepG2 cells with IC_{50} of ($51.28 \pm 3 \mu\text{M}$), ($19.75 \pm 1 \mu\text{M}$) and ($37.06 \pm 2 \mu\text{M}$), respectively, and cisplatin was used as positive controls ($6.58 \pm 3 \mu\text{M}$). Unfortunately, the remained compounds did not show obvious cytotoxicity.

In addition, comparison of the structural characteristics among these compounds, the structure activity relationship is discussed. Compound **2** displayed higher antioxidant activity than compound **1**, which may be due to the additional aldehyde group at C-7 in **2**, which was in agreement with a previous report (Fiorentino et al., 2009). This result might indicate that the aldehyde group is an important functional group that can increase antioxidant capacity. Comparing with the antioxidant activity compound **2**, compound **3** was inactive, which indicated the side chain group at C-2 for the compounds **2** and **3**, were not essential for antioxidant activities.

Conclusion

As a popular cash crop and a traditional herbal medicine, the extract of *D. nobile* Lindl. has been reported to possess antioxidant, anti-tumour, and anti-inflammatory activities. However, the chemical constituents and biological activities of *Dendrobium nobile* have not been elucidated yet. Therefore, in our current study, chemical composition of the extract of *Dendrobium nobile* was isolated and analyzed. Nineteen compounds, including five new compounds (**1–2**, **6–8**) and fourteen known compounds (**3–5**, **9–19**). Antioxidant tests indicated that compound **2** displayed significant antioxidant activity, while compound **19** displayed weak antioxidant activity compared with ascorbic acid (VC). Meanwhile, compound **2** possessed the aldehyde group, which might be an important functional group for antioxidant ability. Besides, the structure-activity relationships (SARs) of tested compounds also suggested that the aldehyde group may play an important role in DPPH radical scavenging. These results implied that the structural variation of vitamin E analogues significantly affected the bioactivity. In addition, compounds **2** and **4** also exhibited an equal effect to positive control cisplatin. Therefore, this research provided a reliable support for *Dendrobium nobile* as potential application in the pharmaceutical and food industries.

Additionally, increasing evidence suggests that oxidative stress plays an important role in the pathogenesis of Alzheimer's disease (AD) (Guidi et al., 2006). Thus, the inhibition of oxidative stress could be a feasible treatment against Alzheimer's disease (AD). Fortunately, studies have shown that natural antioxidants

could exert positive effects against oxidative stress-induced chronic metabolic diseases (Xu et al., 2015). As an important source of natural antioxidants, the *Dendrobium nobile* has attracted much attention in the treatment of AD (Yan et al., 2015). Interestingly, compound **19** not only exhibited antioxidant activity, but also displayed inhibition of NO production, while did not exhibit cytotoxic. The result is consistent with the results reported in the previous literature (Nie et al., 2020). Antioxidant and anti-inflammatory activities are associated with a series of signaling pathways, which may interact with each other in the pathological process of AD (Nie et al., 2020). Therefore, compound **19** might serve as potential lead drug to treat Alzheimer's disease (AD). Findings from this current study provide insights on the phytochemical constituents and significant antioxidant activities of *Dendrobium nobile*, which are critical for the further development for its applications in Alzheimer's disease (AD).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

HL and SZ performed the extraction, isolation and identification, and wrote the manuscript. JL and LZ contributed to the collection and identification the stems of *Dendrobium nobile*. YZ, XF, and SC contributed to this work by bioassay experiments. HN and FL accomplished the ECD calculation. CW and DZ performed revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2022.988459/full#supplementary-material>

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