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ORIGINAL PAPER

The phenolic acids from *Oplopanax elatus* Nakai stems and their potential photo-damage prevention activity

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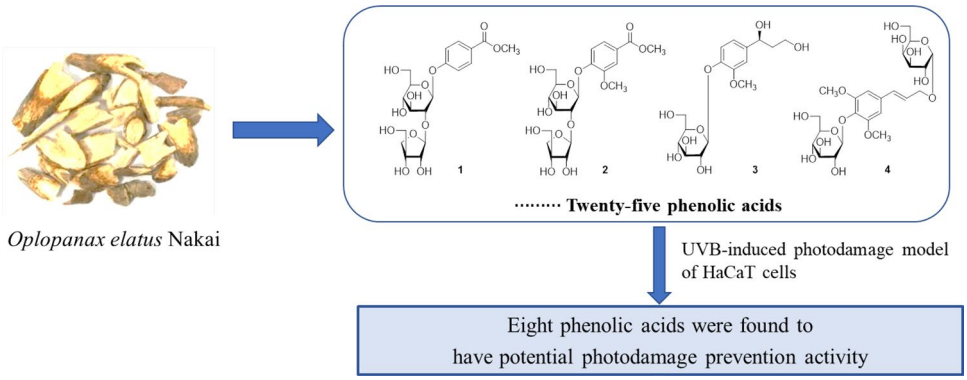
Abstract

25 phenolic acids, including four new isolates, eurylophenosides A–D (**1**–**4**) and 21 known ones (**5**–**25**) were isolated and identified from the stems of *Oplopanax elatus* Nakai. Among the known compounds **5**–**9**, **11**–**13**, **16**, **18**–**25** were isolated from the genus for the first time; **17** was first obtained from the plant; and the NMR data of **22** was reported here first. Meanwhile, the UVB-induced photodamage model of HaCaT cells was used to study the prevent-photodamage abilities of compounds **1**–**2**, **4**–**8**, **11**–**13** and **15**–**25** with a nontoxic concentration at 50 μM. Moreover, a dose-dependent experiment was conducted for active compounds at the concentration of 10, 25, and 50 μM, respectively. Consequently, pretreatment with compounds **1**, **16**, **17**, **19**, **20**, **22**, **24** and **25** could suppress the cell viability decreasing induced by UVB irradiation in a concentration-dependent manner. These results indicated that phenolic acids were one kind of material basis with prevent-photodamage activity of *O. elatus*.

Graphic abstract



Keywords *Oplopanax elatus* Nakai stems · Phenolic acids · Photodamage prevention activity · HaCaT cell

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Introduction

Ultraviolet B (UVB, wavelength 280–320 nm) irradiation can cause various adverse effects, such as sunburn, photoaging, pigmentation, and skin cancer. Preventing UVB interaction or attenuating UVB-related damage could be used to prevent the side effects of UVB irradiation [1]. With the increasing public awareness of the need for health maintenance, it is of great importance to explore new, natural, and effective products to protect against UVB irradiation. Some Chinese herbal medicine, such as *Rhodiola rosea* Limn [2], *Pogostemin cablin* (Blanco) Benth [3], and *Ligusticum chuanxiong* Hort [4], have been confirmed to show the skin protective effects against the photodamage.

Oplopanax elatus Nakai is a deciduous shrub belonging to *Oplopanax* genus, Araliaceae family. It was reported to exhibit various effects, such as anti-fungal, anti-inflammation, anti-oxidant, anti-aging, and anti-radiation [5–11], which suggested that *O. elatus* might have potential anti-photodamage activity. However, the material basis with photodamage prevention activity was still unclear.

Therefore, various chromatographic methods including silica gel, ODS, MCI gel CHP 20P, Sephadex LH-20 column chromatographies (CC) and preparative HPLC chromatography (pHPLC), kinds of spectrophotometric methods including UV, IR, ^{1}H NMR, ^{13}C NMR, ^{1}H ^{1}H COSY, HSQC, HMBC, NOESY, and MS, as well as chemical reaction method were combined to carry out the systematic phytochemical study on the 70% EtOH extract of *O. elatus* stems. In addition, UVB-irradiated human immortalized skin keratinocytes (HaCaT cells) were used to examine the effects of phenolic acids from *O. elatus* stems again UVB-induced skin injury.

Results and discussion

Identification of the chemical constituents from O. elatus stems

The 70% EtOH extract of dried *O. elatus* stems was suspended in water and partitioned with EtOAc (EtOAc-H_2O, 1:1, v/v) to obtain EtOAc layer and H_2O layer. The H_2O layer extract was subjected to D101 macroporous resin CC, and eluated with H_2O and 95% EtOH, successively. Then the 95% EtOH eluated fraction and EtOAc layer extract were separated by silica gel, ODS, MCI gel CHP 20P, Sephadex LH-20 CC, as well as pHPLC. As results, 25 phenolic acids, including four new isolates, eurylophenosides A–D (**1**–**4**, Fig. 1) and 21 known ones, isotachioside (**5**) [12], tachioside (**6**) [12], koaburaside (**7**) [13], 4-(β-D-glucopyranosyloxy)-3-methoxy-benzaldehyde (**8**) [14], 3-methoxyl-4-*O*-β-D-glucopyranosyloxybenzoic acid methyl ester (**9**) [15], caffeic acid (**10**) [16], (*E*)-sinapate 4-*O*-β-glucopyranoside (**11**) [17], 4-*O*-β-D-glucopyranosyl coniferyl aldehyde (**12**) [18], aldeído 4-*O*-β-D-glicopiranosídeo sinápico (**13**) [19], coniferin (**14**) [20], syingin (**15**) [21], (−)-(2*R*)-1-*O*-β-D-glucopyranosyl-2-{2,6-dimethoxy-4-[1-(*E*)-propen-3-ol] phenoxyl}propane-3-ol (**16**) [22], oplopanpheside C (**17**) [23], 4,9-di-*O*-β-D-glucosyl sinapyl alcohol (**18**) [24], 2-methoxy-4-(2-propenyl)phenyl β-D-glucopyranoside (**19**) [25], 4-allyl-2,6-dimethoxyphenyl glucoside (**20**) [26], shashenoside I (**21**) [27], (−)-(2*R*)-1-*O*-(β-D-glucopyranosyl)-2-[2-methoxy-4-(ω-hydroxypropyl)-phenoxyl]-propan-3-ol (**22**) [22, 28], 2,3-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one (**23**) [29], *threo*-guaiacyl glycerol (**24**) [30], *threo*-syringylglycerol (**25**) [31, 32] (Fig. 2) were isolated. Among them, compounds **5**–**9**, **11**–**13**, **16**, **18**–**25** were isolated from the genus for the first time; **17** was first isolated from this plant; and the NMR data of **22** was reported here first.

Eurylophenoside A (**1**) was obtained as white powder, $[\alpha]_D^{25}$ − 132.5 (MeOH). The molecular formula of **1**, $C_{19}H_{26}O_{12}$ (*m/z* 445.13580 $[M - H]^-$; calcd for $C_{19}H_{25}O_{12}$, *m/z* 445.13405) was confirmed by ESI-Q-Orbitrap MS. Its IR spectrum showed characteristic absorptions accounting for hydroxyl (3403 cm^{-1}), ester carbonyl (1707 cm^{-1}), aromatic ring (1607, 1510 cm^{-1}), and ether function (1075 cm^{-1}). The ^{1}H, ^{13}C NMR (Table 1, CD_3OD) spectra of it showed one methoxy signal at δ 3.87 (3H, s, 7-OCH_3); one *p*-disubstituted benzene ring proton signals at δ 7.12 (2H, d, J = 9.0 Hz, H-3,5), 7.96 (2H, d, J = 9.0 Hz, H-2,6); as well as

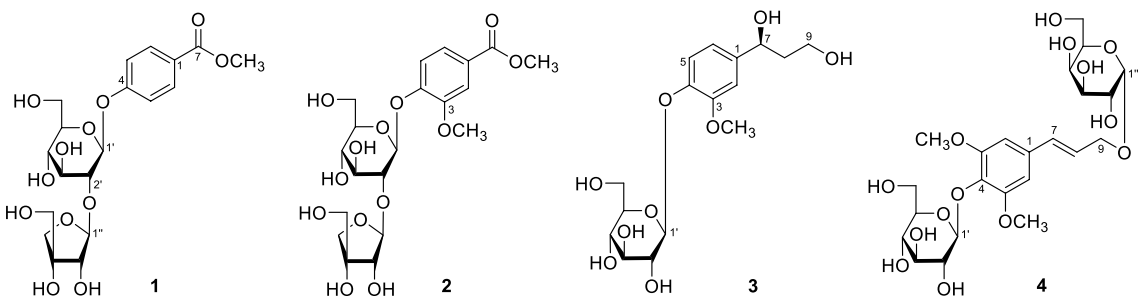

Fig. 1 Structures of new phenolic glycosides **1**–**4** isolated from *O. elatus* stems

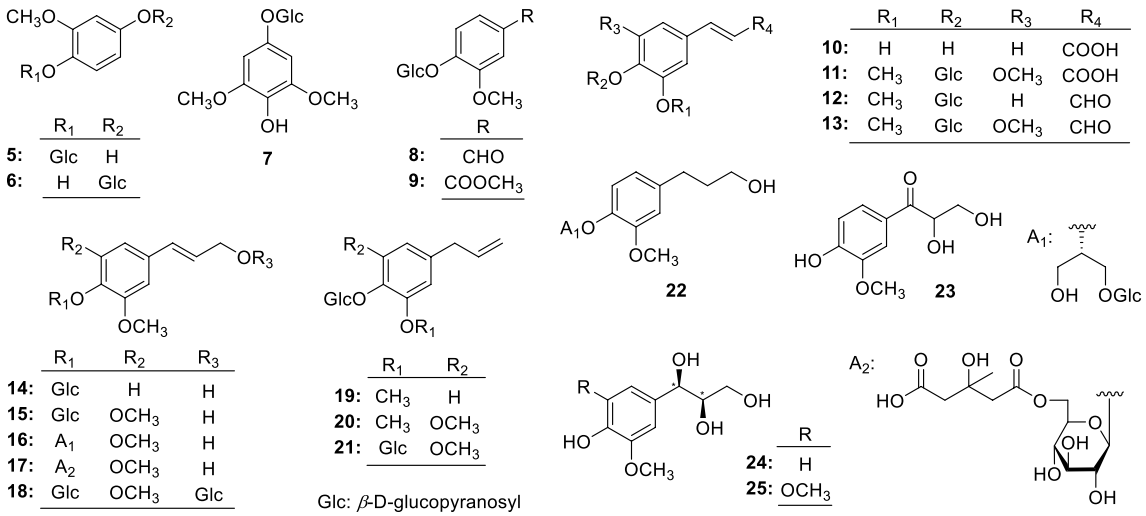

Fig. 2 Structures of known compounds **5**–**25** isolated from *O. elatus* stems

one ester carbonyl carbon signal at δ_C 168.3 (C-7). According to the long-range correlations from δ_H 3.87 (7-OCH_3) to δ_C 168.3 (C-7); δ_H 7.96 (H-2,6) to δ_C 125.1 (C-1), 162.8 (C-4), 168.3 (C-7); δ_H 7.12 (H-3,5) to δ_C 125.1 (C-1), 162.8 (C-4) displayed its HMBC spectrum (Fig. 3), the presence of methyl *p*-hydroxybenzoate group was confirmed. The ^{13}C NMR and mass spectra indicated that **1** was composed of 19 carbon atoms. In addition to the carbon signals represented by the above-mentioned groups, there were still 11 carbon signals in the range of 60–111 ppm had not been assigned. In addition, the existence of one six-carbon sugar and one five-carbon sugar was deduced by combing with two anomeric proton signals at δ 5.08 (1H, d, $J = 8.0$ Hz, H-1′) and 5.46 (1H, d, $J = 1.5$ Hz, H-1″). Acid hydrolysis of **1** produced D-apiose and D-glucose with positive optical rotation [33], which was presumed to be β-D-glucopyranose due to the coupling constant of its anomeric proton ($J = 8.0$ Hz). The correlation from δ_H 5.08 (H-1′) to δ_C 162.8 (C-4) suggested β-D-glucopyranosyl jointed at the 4-position of methyl *p*-hydroxybenzoate. Moreover, the presence of D-apiose acid was further proved by $^3J_{1,2} = 1.5$ Hz (< 4 Hz) of the apiose' anomeric proton (Fig. 3) [33, 34]. In addition, it was clarified to be β-D-apiofuranosyl by the NOE correlations between δ_H 3.94 (H-2″) and δ_H 3.52 (H_2-5″) found in its NOESY experiment, as well as the comparison of the anomeric carbon chemical shift {δ_C 110.9 (C-1″); $\delta_C \sim 104$ ppm (α-D-apiofuranosyl), ~ 110 ppm (β-D-apiofuranosyl) [35, 36]}. Finally, the substituted position of β-D-apiofuranosyl was clarified to be 2-position of β-D-glucopyranosyl according to the correaltion from δ_H 3.67 (H-2′) to δ_C 110.9 (C-1″). Then, the structure of eurylophenoside A (**1**) was elucidated.

Eurylophenoside B (**2**), white powder, $[\alpha]_D^{25}$ − 59.2 (MeOH), was given a molecular formula of $C_{20}H_{28}O_{13}$ based on negative ESI-Q-Orbitrap MS. The ^1H and ^{13}C NMR

Table 1. ^{13}C NMR data for compounds **1–4**

No.	**1**[a]	**2**[b]	**3**[a]	**3a**[c]	**4**[b]	No.	**1**[a]	**2**[b]	**3**[a]	**4**[b]
1	125.1	122.9	141.4	138.7	132.1	1′	100.3	97.9	102.9	102.4
2	132.5	112.2	111.3	110.3	104.4	2′	78.7	74.8	74.9	74.0
3	117.2	148.5	150.8	146.4	152.6	3′	78.6	77.0	77.8	76.4
4	162.8	150.3	147.1	148.2	133.9	4′	71.4	69.7	71.3	69.8
5	117.2	114.2	117.8	115.4	152.6	5′	78.2	76.9	78.2	77.1
6	132.5	122.6	119.6	119.3	104.4	6′	62.5	60.5	62.5	60.7
7	168.3	165.9	72.0	72.8	131.1	1″	110.9	108.3		98.5
8			42.8	43.3	125.8	2″	78.2	76.0		68.3
9			60.1	60.7	67.3	3″	80.7	79.3		69.5
3-OCH_3			56.7	56.3	56.2	4″	75.5	73.9		68.8
5-OCH_3					56.2	5″	66.0	64.4		71.3
7-OCH_3	52.5	51.9				6″				60.7

Determined in [a]CD_3OD, [b]DMSO-d_6, and [c]acetone-d_6

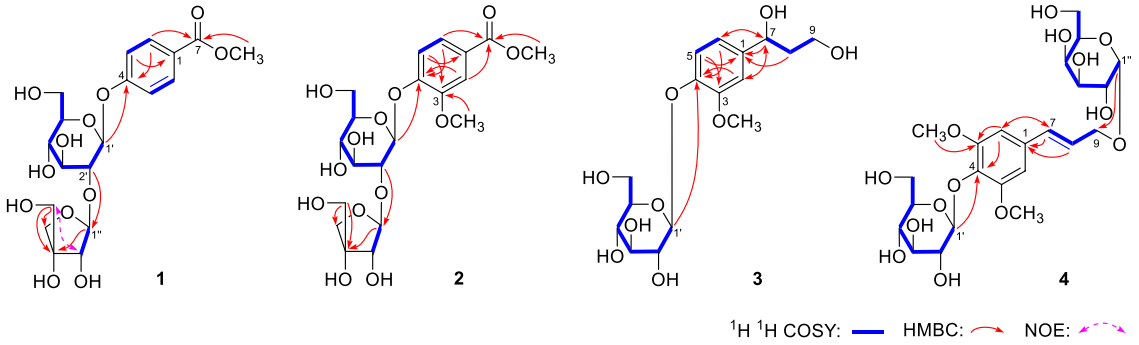

Fig. 3 Main ^{1}H ^{1}H COSY, HMBC correlations of **1–4** and main NOE correlation of **1**

(Table 1, DMSO-d_6) spectra exhibited the same groups, β-D-apiofuranosyl(1 → 2)-β-D-glucopyranosyl [δ 5.13 (1H, d, J = 7.5 Hz, H-1′), 5.44 (1H, br. s, H-1″)], benzene substituted methyl formate [δ_H 3.83 (3H, s, 7-OCH_3); δ_C 51.9 (7-OCH_3), 165.9 (C-7)] as compound **1**. The differences between **2** and **1** were that *p*-disubstituted benzene ring signals disappeared, but one ABX spin-coupling system aromatic proton signals appeared at δ 7.18 (1H, d, J = 8.5 Hz, H-5), 7.49 (1H, d, J = 2.0 Hz, H-2), 7.55 (1H, dd, J = 2.0, 8.5 Hz, H-6) and one more methoxy signals showed at δ 3.83 (3H, s, 3-OCH_3) in **2**. Finally, the structure of eurylophenoside B (**2**) was determined according to the long-range correlations from H-2, H-6 to C-4, C-7; H-5 to C-1, C-3; 3-OCH_3 to C-3; H-1′ to C-4 (Fig. 3).

Eurylophenoside C (**3**) was isolated as white powder with negative optical rotation ($[\alpha]_D^{25}$ − 144.0, MeOH). The ESI-Q-Orbitrap MS spectrum of **3** showed a pseudomolecular ion $[M+COOH]^-$ peak at *m/z* 405.14041 consistent with a molecular formula, $C_{16}H_{24}O_9$. D-glucose was yielded from its acid hydrolysate [33]. The existences of one methoxy [δ 3.86 (3H, s, 3-OCH_3)], one benzene ring with ABX spin-coupled system [δ 6.88 (1H, dd, J = 2.0, 8.0 Hz, H-6), 7.03 (1H, d, J = 2.0 Hz, H-2), 7.12 (1H, d, J = 8.0 Hz, H-5)], together with one β-D-glucopyranosyl [δ 4.87 (1H, d, J = 7.5 Hz, H-1′)] were comfirmed by its ^{1}H and ^{13}C NMR (Table 1, CD_3OD) spectra. The proton and proton correlations between H_2-8 and H-7, H_2-9 showed in the ^{1}H ^{1}H COSY spectrum (Fig. 3) indicated the presence of "–CH–CH_2–CH_2–"moiety. Moreover, the planar structure of **3** was elucidated by the correlations from H-2, H-6 to C-4; H-5 to C-1, C-3; H-7 to C-1, C-2, C-6; H_2-8 to C-1; 3-OCH_3 to C-3; H-1′ to C-4 dispalyed in its HMBC spectrum (Fig. 3). Compound **3** was hydrolyzed by β-glucosidase to obtain its aglycone, 7-hydroxyconiferyl alcohol (**3a**) [37]. Comparing the optical rotation of **3a** ($[\alpha]_D^{25}$ − 20.0, MeOH) with that of 7,8-dihydro-(*R*)-7-methoxyconiferyl alcohol ($[\alpha]_D^{25}$ + 9.0, MeOH) [38], the absolute configuration of eurylophenoside C (**3**) was determined to be 7*S*.

Eurylophenoside D (**4**) was white powder with positive optical rotation ($[\alpha]_D^{25}$ + 12.0, MeOH). ESI-Q-Orbitrap MS determination result {*m/z* 579.19421 $[M+COOH]^-$ (calcd for $C_{24}H_{35}O_{16}$, *m/z* 579.19196)} revealed its molecular formula was $C_{23}H_{34}O_{14}$. D-glucose and D-galactose were obtained when compound **4** was hydrolysed with 1 M HCl [33]. Its ^{1}H, ^{13}C NMR (Table 1, DMSO-d_6) and ^{1}H ^{1}H COSY spectra (Fig. 3) suggested the presences of two methoxy groups [δ 3.78 (6H, s, 3,5-OCH_3)]; one symmetric 1,3,4,5-tetra-substituted benzene ring [δ 6.76 (2H, s, H-2,6)]; one *trans* allyl alcohol moiety [δ 4.09, 4.26 (1H each, both ddd, J = 1.0, 6.0, 14.0 Hz, H_2-9), 6.37 (1H, dt, J = 6.0, 16.0 Hz, H-8), 6.57 (1H, dt, J = 1.0, 16.0 Hz, H-7)]; one β-D-glucopyranosyl [δ 4.92 (1H, d, J = 7.5 Hz, H-1′)]; and one α-D-galactopyranosyl [δ 4.75 (1H, d, J = 3.5 Hz, H-1″)]. Meanwhile, in its HMBC spectrum, the long-range correlations from H-2,6 to C-3,5, C-4, C-7; H-8 to C-1; H-1′ to C-4; 3,5-OCH_3 to C-3,5; H-1″ to C-9 (Fig. 3) were observed. Then, the structure of eurylophenoside D (**4**) was elucidated.

Confirmation of the prevent-photodamage ability of obtained phenolic acids

UVB dose (0, 50, 75, 100, 125 and 150 mJ/cm^2) were selected to irradiate HaCaT cells to confirm the suitable UVB radiation dose [39]. MTT assay results showed that cell viabilities were reduced significantly after 125 mJ/cm^2 UVB irradiation (Fig. S26). Then 125 mJ/cm^2 UVB irradiation was selected to duplicate photodamage model.

To ensure the prevent-photodamage activities of the obtained phenolic acids were determined at nontoxic dose, MTT assay was used to examined the cell viability at 50 μM. As a result, Vc (Vitamin C) and most of compounds (**1**–**2**, **4**–**8**, **11**–**13** and **15**–**25**) were non-cytotoxic at 50 μM on HaCaT cells (Fig. S27).

Among them, HaCaT cells were pretreated with non-cytotoxic compounds at 50 μM for 24 h before UVB irradiation individually. It was found that comparing with no-pretreatment group (Control group), compounds **1**, **16**, **17**, **19**, **20**,

22, **24** and **25** could significantly improve the survival rate of HaCaT cells after UVB irradiation (Table 2). Moreover, the activities of above-mentioned compounds against UVB light injury were in concentration-dependent at 10, 25 and 50 μM (Fig. 4), which suggested that they exhibited potential prevent-photodamage effects on HaCaT cells.

Comparing the prevent-photodamage activities of above-mentioned phenolic acids, the results indicated that the prevent-photodamage effects would enhance with the increase of methoxy substitution (**20** vs **19**, **25** vs **24**).

UVB promotes oxidative stress by inducing reactive oxygen species production and decreasing endogenous antioxidants. To prevent damage generated by UVB irradiation, several studies have focused on compounds or extracts with antioxidant properties [40, 41]. Studies had confirmed that phenolic acids generally had antioxidant activity, which could effectively remove harmful oxygen free radicals in the body, and play the vital of antioxidant damage [42]. In addition, another literature revealed that phenolic compounds (including phenolic acids, flavonols, and anthocyanins) were considered as principal key groups of prevent-photodamage activity [43]. Our study not only clarified those phenolic acids were one kinds of material basis with photodamage prevention activity of *O. elatus*, but also provided guidance for the structural modification of phenolic acids possessed prevent-photodamage activity.

Table 2 Effects of compounds obtained from *O. elatus* stems on prevent-photodamage

No.	Cell viability (%)
Nor	100 ± 2.8***
Con	70.6 ± 3.2
Vc	80.4 ± 3.9***
1	79.3 ± 3.6**
2	71.0 ± 1.7
4	73.3 ± 2.9
5	68.0 ± 2.0
6	60.0 ± 2.5
7	74.6 ± 0.4
8	72.4 ± 1.8
11	66.2 ± 2.6
12	69.1 ± 1.9
13	75.1 ± 0.7
15	69.7 ± 1.1
16	85.8 ± 1.2***
17	93.6 ± 3.4***
18	67.7 ± 1.0
19	77.2 ± 2.1**
20	82.8 ± 2.3***
21	72.7 ± 2.1
22	76.3 ± 1.2*
23	73.5 ± 0.9
24	80.1 ± 3.7**
25	96.5 ± 3.8***

Con UVB-induced HaCaT cell model set. Positive control: Vitamin C (Vc). Cell viability: percentage of normal group (set as 100%). Values represent the mean ± SD of six determinations. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (differences between other groups vs Con group). Final concentration was 50 μM for Vc and all compounds

Experimental

Experimental procedures for phytochemistry study

Experimental materials and instrument

NMR spectra were determined on Bruker ascend 600 MHz and/or Bruker ascend 500 MHz NMR spectrometer (Bruker BioSpin AG Industriestrasse 26 CH-8117, Fällanden, Switzerland) with tetramethylsilane as an internal standard. Negative-ion and positive-ion mode ESI-Q-Orbitrap MS were measured on a Thermo ESI-Q-Orbitrap MS mass spectrometer connected to the UltiMate 3000 UHPLC instrument via ESI interface (Thermo, Waltham, MA). Optical rotations, UV and IR spectra were run on a Rudolph Autopol® IV automatic polarimeter (l = 50 mm) (Rudolph Research Analytical, Hackettstown NJ, USA), Varian Cary 50 UV–Vis (Varian, Inc., Hubbardsdon, MA, USA) and Varian 640-IR FT-IR spectrophotometer (Varian Australia Pty Ltd., Mulgrave, Australia), respectively.

Column chromatorgtaphies (CC) were performed on macroporous resin D101 (Haiguang Chemical Co., Ltd., Tianjin, China), silica gel (48–75 μm, Qingdao Haiyang Chemical Co., Ltd., Qingdao, China), ODS (50 μm, YMC Co., Ltd., Tokyo, Japan), MCI gel CHP 20P (Mitsubishi Chemical Corporation, CHP20/P120, Japan), and Sephadex LH-20 (Ge Healthcare Bio-Sciences, Uppsala, Sweden). HPLC column: Cosmosil 5C_{18}-MS-II and Cosmosil PBr column (both 4.6 mm i.d. × 250 mm, 5 μm, Nakalai Tesque, Inc., Tokyo, Japan) were used to analysis, and Cosmosil 5C_{18}-MS-II and Cosmosil PBr column (20 mm i.d. × 250 mm, 5 μm, Nakalai Tesque, Inc., Tokyo, Japan) were used to separate the constituents. Venusil PrepG C18 column (250 mm × 50 mm, 10 μm, Agela technologies, Tianjin, China)].

Dichloromethane (CH_2Cl_2), methanol (MeOH), acetonitrile (CH_3CN), acetic acid (HAc) and other reagents (chromatographically pure or analytical pure) were purchased from Tianjin Concord Technology Co., Ltd.

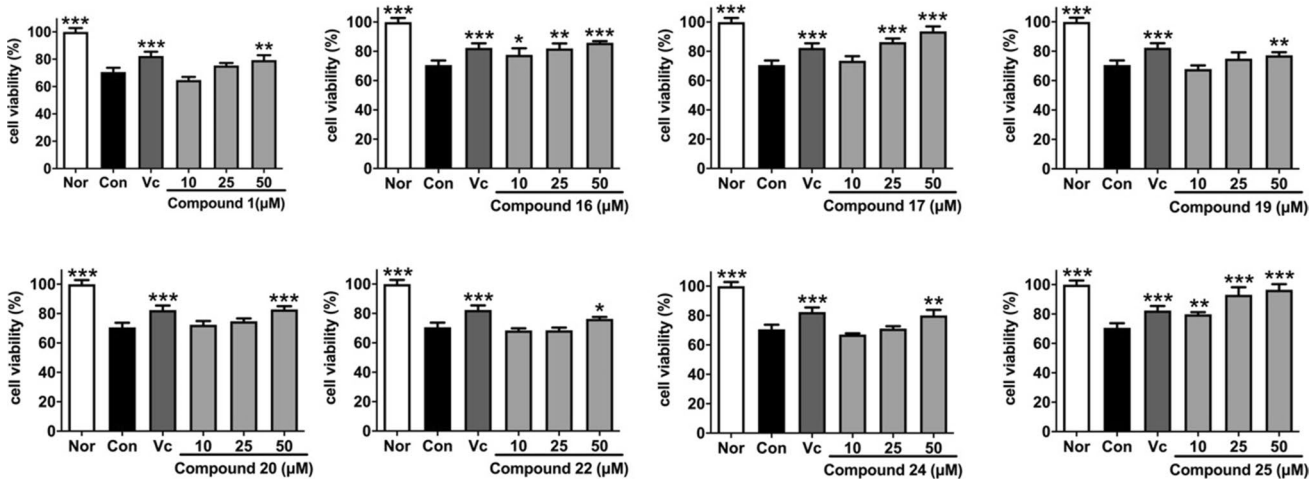

Fig. 4 Effects of compounds **1**, **16**, **17**, **19**, **20**, **22**, **24**, and **25** at concentration of 10, 25, 50 μM on HaCaT cell viability Nor: normal group without UVB-induced, V_C, and other tested samples. Con: UVB-induced model set. Values represent the mean ± SD of six determinations. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (differences between other groups vs Con group)

Plant material

The stems of *O. elatus* were collected from Tonghua city, Jilin province, China, identified by Professor Junyi Zhu (Tonghua Normal University). The voucher specimen was deposited at the Academy of Traditional Chinese Medicine of Tianjin University of TCM.

Extraction and isolation

The dried stems of *O. elatus* (5.5 kg) were extracted three times with 70% EtOH under reflux for 3 h, 3 h, 2 h, successively. Evaporation of the extractions under reduced pressure to yield 70% EtOH extracts (815.0 g), which (710.0 g) was partitioned in an EtOAc–H_2O mixture (1:1, v/v) three times to obtain H_2O layer (404.0 g) and EtOAc layer (300.7 g). H_2O layer (383.8 g) was subjected to D101 macroporous resin CC ($H_2O \rightarrow$ 95% EtOH) to gain H_2O (300.0 g) and 95% EtOH (72.0 g) eluates.

95% EtOH eluate (70.0 g) was subjected to silica gel CC [CH_2Cl_2–MeOH (100:0 → 100:1 → 100:3 → 100:7 → 10:1 → 20:3 → 5:1 → 3:1 → 1:1 → 0:100, v/v)] to give Fr. 1–Fr. 12. Fraction 4 (628.0 mg) was separated by pHPLC [MeOH-1% HAc (80:20, v/v), $5C_{18}$-MS-II column] to gain 2,3-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one (**23**, 4.0 mg). Fraction 7 (3.4 g) was isolated by MCI gel CHP 20P CC [MeOH–H_2O (10:90 → 20:80 → 30:70 → 40:60 → 50:50 → 60:40 → 70:30 → 80:20 → 100:0, v/v)] to obtain Fr. 7-1–Fr. 7-8. Fraction 7-2 (81.5 mg) was purified by pHPLC [MeOH-1% HAc (20:80, v/v), Cosmosil PBr column], then *threo*-guaiacyl glycerol (**24**, 10.6 mg) and *threo*-syringylglycerol (**25**, 10.0 mg) were given. Fraction 7-4 (348.5 mg) was separated by pHPLC [MeOH-1% HAc (40:60, v/v), Cosmosil PBr column] to provide Fr. 7-4-1–Fr. 7-4-10. Fraction 7-4-4 (36.0 mg) was purified by pHPLC [CH_3CN-1% HAc (10:90, v/v), Cosmosil $5C_{18}$-MS-II column] to obtain 4-(β-D-glucopyranosyloxy)-3-methoxy-benzaldehyde (**8**, 5.0 mg). Fraction 7-5 (596.8 mg) was isolated by pHPLC [MeOH-1% HAc (20:80, v/v), Cosmosil $5C_{18}$-MS-II column], and 14 fractions (Fr. 7-5-1–Fr. 7-5-14) were yielded. Fraction 7-5-7 was identified as 4-*O*-β-D-glucopyranosyl coniferyl aldehyde (**12**, 21.6 mg). Fraction 7-5-11 (30.4 mg) was purified by pHPLC [MeOH-1% HAc (55:45, v/v), Cosmosil PBr column] to get aldeído 4-*O*-β-D-glicopiranosídeo sinápico (**13**, 17.3 mg). Fraction 7-7 (1.2 g) was separated by pHPLC [CH_3CN-1% HAc (20:80, v/v), Cosmosil $5C_{18}$-MS-II column] to yield Fr. 7-7-1–Fr. 7-7-9. Fraction 7-7-7 (52.7 mg) was isolated by pHPLC [MeOH-1% HAc (40:60, v/v), Cosmosil $5C_{18}$-MS-II column] to provide 2-methoxy-4-(2-propenyl)phenyl β-D-glucopyranoside (**19**, 12.0 mg) and 4-allyl-2,6-dimethoxyphenyl glucoside (**20**, 6.0 mg). Fraction 8 (16.0 g) was subjected to ODS CC [MeOH–H_2O (10:90 → 20:80 → 30:70 → 40:60 → 50:50 → 100:0, v/v)], and Fr. 8-1–Fr. 8-13 were given. Fraction 8-2 (392.5 mg) was separated by pHPLC [MeOH-1% HAc (20:80, v/v), Cosmosil PBr column] to gain Fr. 8-2-1–Fr. 8-2-8. Fraction 8-2-3 (64.5 mg) was purified by pHPLC [CH_3CN-1% HAc (5:95, v/v), Cosmosil $5C_{18}$-MS-II column] to provide tachioside (**6**, 34.8 mg). Fraction 8-2-5 (51.5 mg) was isolated by pHPLC [CH_3CN-1% HAc (5:95, v/v), Cosmosil $5C_{18}$-MS-II column], as result, isotachioside (**5**, 19.3 mg) and koaburaside (**7**, 15.0 mg) were yielded. Fraction 8-5 (800.0 mg) was separated by pHPLC [MeOH-1% HAc (20:80, v/v), Cosmosil $5C_{18}$-MS-II column], and six fractions (Fr.

8-5-1–Fr. 8-5-6) were given. Fractions 8-5-1 and 8-5-3 were identified as coniferin (**14**, 34.4 mg) and syingin (**15**, 75.1 mg), respectively. Fraction 8-6 (604.3 mg) were subjected to pHPLC [CH_3CN-1% HAc (10:90, v/v), Cosmosil $5C_{18}$-MS-II column] to provide Fr. 8-6-1–Fr. 8-6-8. Fraction 8-6-2 (185.1 mg) was purified by pHPLC [MeOH-1% HAc (20:80, v/v), Cosmosil $5C_{18}$-MS-II column] to get (*E*)-sinapate 4-*O*-β-glucopyranoside (**11**, 18.2 mg). Fraction 8-7 (1.3 g) was separated by pHPLC [CH_3CN-1% HAc (10:90, v/v), Cosmosil $5C_{18}$-MS-II column] to get Fr. 8-7-1–Fr. 8-7-11. Fraction 8-7-7 (168.3 mg) was isolated by pHPLC [MeOH-1% HAc (40:60, v/v), Cosmosil PBr column] to give eurylophenoside (**1**, 12.1 mg) and (−)-(2*R*)-1-*O*-β-D-glucopyranosyl-2-{2,6-dimethoxy-4-[1-(*E*)-propen-3-ol]phenoxyl}propane-3-ol (**16**, 45.2 mg). Fraction 8-7-8 (252.2 mg) was prepared by pHPLC [MeOH-1% HAc (40:60, v/v), Cosmosil PBr column] to provide 3-methoxyl-4-*O*-β-D-glucopyranosyloxybenzoic acid methyl ester (**9**, 11.6 mg) and eurylophenoside B (**2**, 145.3 mg). Fraction 8-7-9 (99.6 mg) was purified by pHPLC [MeOH-1% HAc (45:55, v/v), Cosmosil PBr column], and oplopanpheside C (**17**, 30.0 mg) was yielded. Fraction 10 (11.0 g) was subjected to ODS CC [MeOH–H_2O (10:90 → 20:80 → 30:70 → 40:60 → 50:50 → 60:40 → 100:0, v/v)], and nine fractions (Fr. 10-1–Fr. 10-9) were given. Fraction 10-2 (434.5 mg) was purified by pHPLC [MeOH-1% HAc (13:87, v/v) and CH_3CN-1% HAc (5:95, v/v), $5C_{18}$-MS-II column] to provide eurylophenoside C (**3**, 27.3 mg). Fraction 10-6 (581.1 mg) was isolated by pHPLC [MeOH-1% HAc (25:75, v/v) and CH_3CN-1% HAc (11:89, v/v), $5C_{18}$-MS-II column], and (−)-(2*R*)-1-*O*-(β-D-glucopyranosyl)-2-[2-methoxy-4-(ω-hydroxypropyl)-phenoxyl]-propan-3-ol (**22**, 6.3 mg) was given. Fraction 10-7 (998.0 mg) was purified by pHPLC [MeOH-1% HAc (27:73, v/v), $5C_{18}$-MS-II column] to yield shashenoside I (**21**, 17.0 mg). Fraction 11 (6.4 g) was prepared by pHPLC [MeOH-1% HAc (15:85 → 50:50 → 100:0, v/v), Venusil PrepG C_{18} column], and [MeOH-1% HAc (35:65, v/v), Cosmosil PBr column] to give eurylophenoside D (**4**, 14.2 mg) and 4,9-di-*O*-β-D-glucosyl sinapyl alcohol (**18**, 11.1 mg).

EtOAc layer (150.0 g) was subjected to silica gel CC [PE-CH_2Cl_2 (8:1 → 3:1 → 0:100, v/v) → CH_2Cl_2-MeOH (100:1 → 100:3 → 100:7 → 10:1 → 0:100, v/v)], and Fr. E-1–Fr. E-15 were provided. Fraction E-12 (11.1 g) was separated by Sephadex LH-20 CC (MeOH) and pHPLC [CH_3CN-1% HAc (20:80, v/v), Cosmosil $5C_{18}$-MS-II column] to give caffeic acid (**10**, 10.0 mg).

Eurylophenoside A (*1*)

White powder; $[\alpha]_D^{25}$ − 132.5 (*conc* 0.25, MeOH); UV λ_{max} (MeOH) nm (log ε): 250 (4.11); IR ν_{max} (KBr) cm^{-1}: 3403, 2949, 2887, 1707, 1607, 1510, 1437, 1291, 1246, 1075; ^1H NMR (CD_3OD, 500 MHz) δ: 7.96 (2H, d, J = 9.0 Hz, H-2,6), 7.12 (2H, d, J = 9.0 Hz, H-3,5), 5.08 (1H, d, J = 8.0 Hz, H-1′), 3.67 (1H, dd, J = 8.0, 9.0 Hz, H-2′), 3.62 (1H, dd, J = 9.0, 9.0 Hz, H-3′), 3.41 (1H, dd, J = 9.0, 9.5 Hz, H-4′), 3.48 (1H, m, H-5′), [3.70 (1H, dd, J = 5.5, 12.0 Hz), 3.89 (1H, dd, J = 2.5, 12.0 Hz), H_2-6′], 5.46 (1H, d, J = 1.5 Hz, H-1″), 3.94 (1H, d, J = 1.5 Hz, H-2″), 3.79, 4.02 (1H each, both d, J = 9.5 Hz, H_2-4″), 3.52 (2H, s, H_2-5″), 3.87 (3H, s, 7-OCH_3); ^{13}C NMR (CD_3OD, 125 MHz) δ: Table 1; ESI-Q-Orbitrap MS (*m/z* 445.13580 $[M - H]^-$; calcd for $C_{19}H_{25}O_{12}$, 445.13405).

Eurylophenoside B (*2*)

White powder; $[\alpha]_D^{25}$ − 59.2 (*conc* 0.50, MeOH); UV λ_{max} (MeOH) nm (log ε): 256 (4.07), 294 (3.70); IR ν_{max} (KBr) cm^{-1}: 3405, 2949, 2887, 1711, 1607, 1510, 1437, 1291, 1246, 1075; ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.49 (1H, d, J = 2.0 Hz, H-2), 7.18 (1H, d, J = 8.5 Hz, H-5), 7.55 (1H, dd, J = 2.0, 8.5 Hz, H-6), 5.13 (1H, d, J = 7.5 Hz, H-1′), 3.60 (1H, dd, J = 7.5, 8.0 Hz, H-2′), 3.52 (1H, dd, J = 8.0, 8.5 Hz, H-3′), 3.23 (1H, dd, J = 8.5, 9.0 Hz, H-4′), 3.43 (1H, m, H-5′), [3.49 (1H, dd, J = 5.5, 12.0 Hz), 3.71 (1H, br. d, *ca*. J = 12 Hz), H_2-6′], 5.44 (1H, br. s, H-1″), 3.79 (1H, br. s, H-2″), 3.63, 4.05 (1H each, both d, J = 9.5 Hz, H_2-4″), 3.29 (2H, s, H_2-5″), 3.83 (6H, s, 3, 7-OCH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: Table 1; ESI-Q-Orbitrap MS (*m/z* 475.14636 $[M - H]^-$; calcd for $C_{20}H_{27}O_{13}$, 475.14462).

Eurylophenoside C (*3*)

White powder; $[\alpha]_D^{25}$ − 144.0 (*conc* 1.20, MeOH); UV λ_{max} (MeOH) nm (log ε): 225 (3.99), 277 (3.52); IR ν_{max} (KBr) cm^{-1}: 3384, 2913, 1598, 1514, 1423, 1264, 1226, 1075; ^1H NMR (CD_3OD, 500 MHz) δ: 7.03 (1H, d, J = 2.0 Hz, H-2), 7.12 (1H, d, J = 8.0 Hz, H-5), 6.88 (1H, dd, J = 2.0, 8.0 Hz, H-6), 4.75 (1H, dd, J = 5.0, 8.0 Hz, H-7), 1.84, 1.95 (1H each, both m, H_2-8), 3.58, 3.67 (1H each, both dt, J = 6.5, 12.5 Hz, H_2-9), 4.87 (1H, d, J = 7.5 Hz, H-1′), 3.49 (1H, dd, J = 7.5, 9.0 Hz, H-2′), 3.46 (1H, dd, J = 9.0, 9.0 Hz, H-3′), 3.39 (2H, m, overlapped, H-4′ and H-5′), [3.68 (1H, dd, J = 4.5, 12.0 Hz), 3.86 (1H, dd, J = 1.5, 12.0 Hz), H_2-6′], 3.86 (3H, s, 3-OCH_3); ^{13}C NMR (CD_3OD, 125 MHz) δ: Table 1; ESI-Q-Orbitrap MS (*m/z* 405.14041 $[M+COOH]^-$; calcd for $C_{17}H_{25}O_{11}$, 405.13914).

Eurylophenoside D (*4*)

White powder; $[\alpha]_D^{25}$ + 12.0 (*conc* 0.10, MeOH); UV λ_{max} (MeOH) nm (log ε): 221 (4.17), 268 (3.89); IR ν_{max} (KBr) cm^{-1}: 3309, 2949, 2923, 1560, 1418, 1337, 1246, 1121, 1071, 842; ^1H NMR (DMSO-d_6, 500 MHz) δ: 6.76 (2H,

s, H-2,6), 6.57 (1H, dt, J = 1.0, 16.0 Hz, H-7), 6.37 (1H, dt, J = 6.0, 16.0 Hz, H-8), 4.09, 4.26 (1H each, both ddd, J = 1.0, 6.0, 14.0 Hz, H_2-9), 4.92 (1H, d, J = 7.5 Hz, H-1′), 3.20 (2H, m, overlapped, H-2′ and H-3′), 3.14 (1H, dd, J = 9.0, 9.5 Hz, H-4′), 3.03 (1H, ddd, J = 2.0, 5.5, 9.0 Hz, H-5′), [3.41 (1H, dd, J = 5.5, 11.0 Hz), 3.58 (1H, dd, J = 2.0, 11.0 Hz), H_2-6′], 4.75 (1H, d, J = 3.5 Hz, H-1″), 3.63 (1H, dd, J = 3.5, 3.5 Hz, H-2″), 3.57 (1H, dd, J = 3.0, 6.0 Hz, H-3″), 3.72 (1H, br. d, *ca*. J = 2 Hz, H-4″), 3.65 (1H, t like, *ca*. J = 6 Hz, H-5″), [3.49 (1H, dd, J = 7.0, 11.0 Hz), 3.53 (1H, dd, J = 5.5, 11.0 Hz), H_2-6″], 3.78 (6H, s, 3,5-OCH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: Table 1; ESI-Q-Orbitrap MS (*m/z* 579.19421 $[M+COOH]^-$; calcd for $C_{24}H_{35}O_{16}$, 579.19196).

(−)-(2R)-1-O-(β-D-glucopyranosyl)-2-[2-methoxy-4-(ω-hydroxypropyl)-phenoxyl]-propan-3-ol (22)

White powder; $[\alpha]_D^{25}$ − 12.5 (*conc* 0.25, in MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ: 6.85 (1H, d, J = 2.0 Hz, H-2), 7.01 (1H, d, J = 8.0 Hz, H-5), 6.73 (1H, dd, J = 2.0, 8.0 Hz, H-6), 2.62 (2H, t, J = 8.0 Hz, H_2-7), 1.81 (2H, m, H_2-8), 3.56 (2H, t, J = 6.5 Hz, H_2-9), [3.79 (1H, dd, J = 5.5, 12.0 Hz), 3.84 (1H, dd, J = 7.0, 12.0 Hz), H_2-1′], 4.34 (1H, m, H-2′), 3.83, 4.06 (1H each, both dd, J = 4.5, 11.0 Hz, H_2-3′), 4.32 (1H, d, J = 8.0 Hz, H-1″), 3.20 (1H, dd, J = 8.0, 9.0 Hz, H-2″), 3.35 (1H, dd, J = 8.5, 9.0 Hz, H-3″), 3.28 (1H, dd, J = 8.5, 8.5 Hz, H-4″), 3.26 (1H, m, H-5″), [3.65 (1H, dd, J = 5.0, 12.0 Hz), 3.82 (1H, dd, J = 2.0, 12.0 Hz), H_2-6″], 3.83 (3H, s, 3-OCH_3); ^{13}C NMR (CD_3OD, 125 MHz) δ: 138.4 (C-1), 114.0 (C-2), 151.9 (C-3), 146.5 (C-4), 119.3 (C-5), 121.8 (C-6), 32.8 (C-7), 35.6 (C-8), 62.2 (C-9), 68.9 (C-1′), 81.3 (C-2′), 62.1 (C-3′), 104.8 (C-1″), 75.1 (C-2″), 78.0 (C-3″), 71.6 (C-4″), 78.0 (C-5″), 62.6 (C-6″), 56.4 (3-OCH_3); ESI-Q-Orbitrap MS (*m/z* 463.18253 $[M+COOH]^-$; calcd for $C_{20}H_{31}O_{12}$, *m/z* 463.18100). The NMR data of it was reported first.

Enzyme hydrolysis of compound *3*

Compund **3** (6.0 mg) and β-glucosidase (6.0 mg, Lot BCBW3258, Sigma company) were mixed, and dissolved in 1.0 mL distilled water. The reaction was carried out for 5 h at 37 °C. The reaction solution was extracted with EtOAc, and 7*S*-hydroxyconiferyl alcohol (**3a**, 1.9 mg) was obtained.

7S-hydroxyconiferyl alcohol (*3a*)

White powder; $[\alpha]_D^{25}$ − 20.0 (*conc* 0.05, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ: 6.99 (1H, d, J = 1.8 Hz, H-2), 6.76 (1H, d, J = 7.8 Hz, H-5), 6.80 (1H, dd, J = 1.8, 7.8 Hz, H-6), 4.78 (1H, dt, J = 3.0, 6.6 Hz, H-7), 1.81, 1.90 (1H each, both m, H_2-8), 3.70 (2H, dt, J = 5.4, 10.8 Hz, H_2-9), 3.84 (3H, s, 3-OCH_3); ^{13}C NMR (Acetone-d_6, 150 MHz) δ: Table 1; ESI-Q-Orbitrap MS (*m/z* 197.08118 $[M-H]^-$; calcd for $C_{10}H_{13}O_4$, 197.08084).

Acid hydrolysis of *1–4*

A solution of compounds **1**–**4** (1.0 mg each) in 1 M HCl (1 mL) was heated under reflux, the reaction product was treated using the similar method as previously reported [33]. The hydrolysis products were analysed using HPLC [column: Kaseisorb LC NH_2-60-5, 4.6 mm i.d. × 250 mm (Tokyo Kasei Co., Ltd., Tokyo, Japan); mobile phase: CH_3CN–H_2O (80:20, v/v); flow rate: 0.7 mL/min)]. As results, D-glucose (t_R: 12.2 min, positive optical rotation) for **1**–**4**, D-apiose (t_R: 8.5 min, positive optical rotation) for **1** and **2**, as well as D-galactose (t_R: 7.2 min, positive optical rotation) for **4** were identified by comparing their retention time and optical rotation with those of authentic samples.

Experimental procedures for bioassay

Materials

BioTek Cytation five-cell imaging multi-mode reader (Winooski, VT, USA) was used to measure cell viability; UVB radiation machine (SH4B, Sigma, Shanghai, China) and UVB Radiometer (ST90-UVB, 297 nm, Beijing, China) were used to test light damage model and radiation dose, respectively; HaCaT cell lines were gained from Procell Life Science&Technology Co., Ltd. (Wuhan, China); Fetal Bovine Serum (FBS) was obtained from Biological Industries (Beit-Haemek, Israel); Minimum Essential Medium (MEM) was ordered from Corning (Shanghai, China); Penicillin and streptomycin were purchased from Thermo Fisher Scientific (Waltham, MA, USA); MTT and Dimethyl sulfoxide (DMSO) were gained from Sigma-Aldrich (St. Louis, MO, USA); Vitamin C (Vc) were got from Shanghai Yuanye Bio-Technology Co., Ltd (Shanghai, China).

Cell culture

HaCaT cells were maintained in MEM with 10% FBS, streptomycin (100 μg/mL), penicillin (100 U/mL), and maintained at 5% CO_2 at 37 °C. When the cells grew to 80% confluence, they were seeded at 1×10^4 cells/well in 96-well plates, and then processed the treatment.

Cell viability assay

Cell viability were assayed by MTT assay. HaCaT cells were incubated at 96-well plates and treated without or

with test samples (50 μM) for 24 h, respectively. The culture condition was the same as "Cell culture". The medium was removed, 1% MTT (5 mg/mL) were added into wells to formate formazan. After 4 h incubation, the supernatant was removed. Then 100 μL dimethyl sulfoxide (DMSO) was added in every well to dissolve the formated formazan. The absorbance at 490 nm was measured with a microplate reader.

The selection of UVB radiation dose

The HaCaT cells were cultured in a 96-well plate until grown to 80% confluence, and covered with fresh medium containing for 24 h. Then the complete medium was removed and 100 μL PBS per well was added. Then the HaCaT cells were exposed to 50, 75, 100, 125 and 150 mJ/cm^2 of UVB. The dose of UVB radiation was measured by UV radiometer. After irradiation, the 100 μL fresh medium were covered per well, incubated 24 h. The cell viability assay was tested according to "Cell viability assay".

Prevent-photodamage ability of isolated phenolic acids

HaCaT cells were incubated in 96-well plates with complete medium until grown to 80% confluence, and covered with fresh medium containing various concentrations of samples (10, 25 and 50 μM) for 24 h. Then, replaced by 100 μL PBS, and the cells were irradiated with UVB at 125 mJ/cm^2. After irradiation, the PBS was replaced by 100 μL fresh medium and incubated 24 h continuing. Finally, the cell viability assay was measured according to "Cell viability assay".

Statistical analysis

All experiments were repeated six times, and the results are presented as the means ± standard deviation (SD). SPSS 17.0 was used to conduct the statistics of all the grouped data. $P < 0.05$ was considered to indicate statistical significance. One-way analysis of variance (ANOVA) and Tukey's studentized range test were used for the evaluation of the significant differences between means and post hoc, respectively.

Conclusions

In summary, four new phenolic acids, eurylophenosides A–D (**1**–**4**), together with 21 known ones (**5**–**25**) were obtained from *O. elatus* stems. Their structures were elucidated using various spectral techniques and chemical reactions. Among the known isolates **5**–**9**, **11**–**13**, **16**, **18**–**25** were isolated from the genus for the first time, **17** was first isolated from this plant. In addition, the NMR data of **22** was reported here first.

Moreover, HaCaT cells were pretreated by compounds **1**, **16**, **17**, **19**, **20**, **22**, **24** as well as **25** for 24 h, the survival rate of HaCaT cells after UVB irradiation will increase significantly. The result confirmed that phenolic acids were one kinds of the material basis with prevent-photodamage activity of *O. elatus*. In addition, it would provide a theoretical basis for the development of *O. elatus* stems as a photoprotective product.

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