Chemical Constituents of *Pedicularis densispica* Franch

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An ethanol extract of the dried aerial of *Pedicularis densispica* Franch (Scrophulariaceae) afforded a new lignan, densispicoside (**1**), and two new iridoids, densispicnin C and D (**14**, **15**), together with four lignans, (+)-isolarisiresinol 3a-*O*-β-D-glucopyranoside (**2**), (–)-pinoresinol-β-D-glucopyranoside (**3**), syringaresinol mono-β-D-glucopyranoside (**4**), longifloroside B (**5**), eight phenylpropanoids, 4-*O*-β-D-glucopyranosyl-sinapic acid methyl ester (**6**), 3-(4-hydroxy-3-methoxyphenyl)-1,2,3-propantriol (**7**), citrusin C (**8**), robustaside B (**9**), verbascoside (**10**), martynoside (**11**), 2″-*O*-acetylverbascoside (**12**), *cis*-martynoside (**13**), and two iridoid glycosides, shanzhiside methyl ester (**16**), and 8-epiloganin (**17**). Their structures were established on the basis of chemical and spectroscopic studies. Bioactivity results indicate that *P. densispica* shows activity on PAI-1 antithrombus assay *in vitro* and antifatigue activities *in vivo*.

Key words: Scrophulariaceae, *Pedicularis densispica*, Densispicoside, Densispicnin C and D

Introduction

In China, the genus *Pedicularis* (Scrophulariaceae) is represented by 329 species [1]. Of these, many have been used in the traditional Chinese medicines to treat diuresis, exhaustion, collapse, and senility [2]. Pharmacological studies on phenylpropanoids from *Pedicularis* showed that they had strong scavenging effects on superoxide and anti-oxidant effects [3, 4]. In a previous paper [5], we have reported the isolation and structure elucidation of iridoids from *P. densispica*. From our current research of this plant, we now report the isolation and structure elucidation of three new compounds, densispicoside (**1**), densispicnin C (**14**), and densispicnin D (**15**), obtained along with fourteen known compounds (Fig. 1). In addition, we also report on the biological activities of *P. densispica*.

Results and Discussion

Compounds **2** – **13**, **16** – **17** were identified spectroscopically as (+)-isolarisiresinol 3a-*O*-β-D-glucopyranoside (**2**) [6], (–)-pinoresinol-β-D-glucopyranoside (**3**) [7], syringaresinol mono-β-D-glucopyranoside (**4**) [8], longifloroside B (**5**) [9], 4-*O*-β-D-glucopyranosyl-sinapic acid methyl ester (**6**) [10], 3-(4-hydroxy-3-methoxy-phenyl)-1,2,3-propantriol (**7**) [11], citrusin C (**8**) [12], robustaside B (**9**) [13], verbascoside (**10**) [14], martynoside (**11**) [15], 2″-*O*-acetylverbascoside (**12**) [16], *cis*-martynoside (**13**) [17], shanzhiside methyl ester (**16**) [18], and 8-epiloganin (**17**) [19].

Compound **1** was obtained as a colorless amorphous powder. The molecular formula of **1** was determined to be $C_{26}H_{34}O_{11}$ by negative ion HR-TOF-MS (m/z = 521.2021, calcd. 521.2022, $[M–1]^-$). The IR spectrum (KBr) showed absorptions for hydroxyl groups (3419 cm^{-1}), aromatic rings (1610, 1513 cm^{-1}) and ether functions (1077, 1033 cm^{-1}). A comparison of the proton and carbon signals in the ^1H and ^{13}C NMR spectra of **1** with that of (+)-isolarisiresinol 3a-*O*-β-D-glucopyranoside (**2**) [6] indicated that they had similar structures (see Table 1). The anomeric proton of glucose at δ_H = 4.26 (1H, d, J = 8.0 Hz, H-1″) suggested that the glucose was in β-orientation. The sugar linkage was determined on the basis of HMBC experiments (Fig. 2). A cross peak of ^1H, ^{13}C long range coupling was observed between the proton signal at δ_H = 4.26 (1H, d, J = 8.0 Hz, H-1″ of Glc) and the carbon signal at δ_C = 71.7 (CH_2, C-3a), indicating that the β-D-glucose was linked at C-3a. Correlations between δ_H = 2.25 (1H, m, H-3) and δ_H = 2.67 (1H, dd,

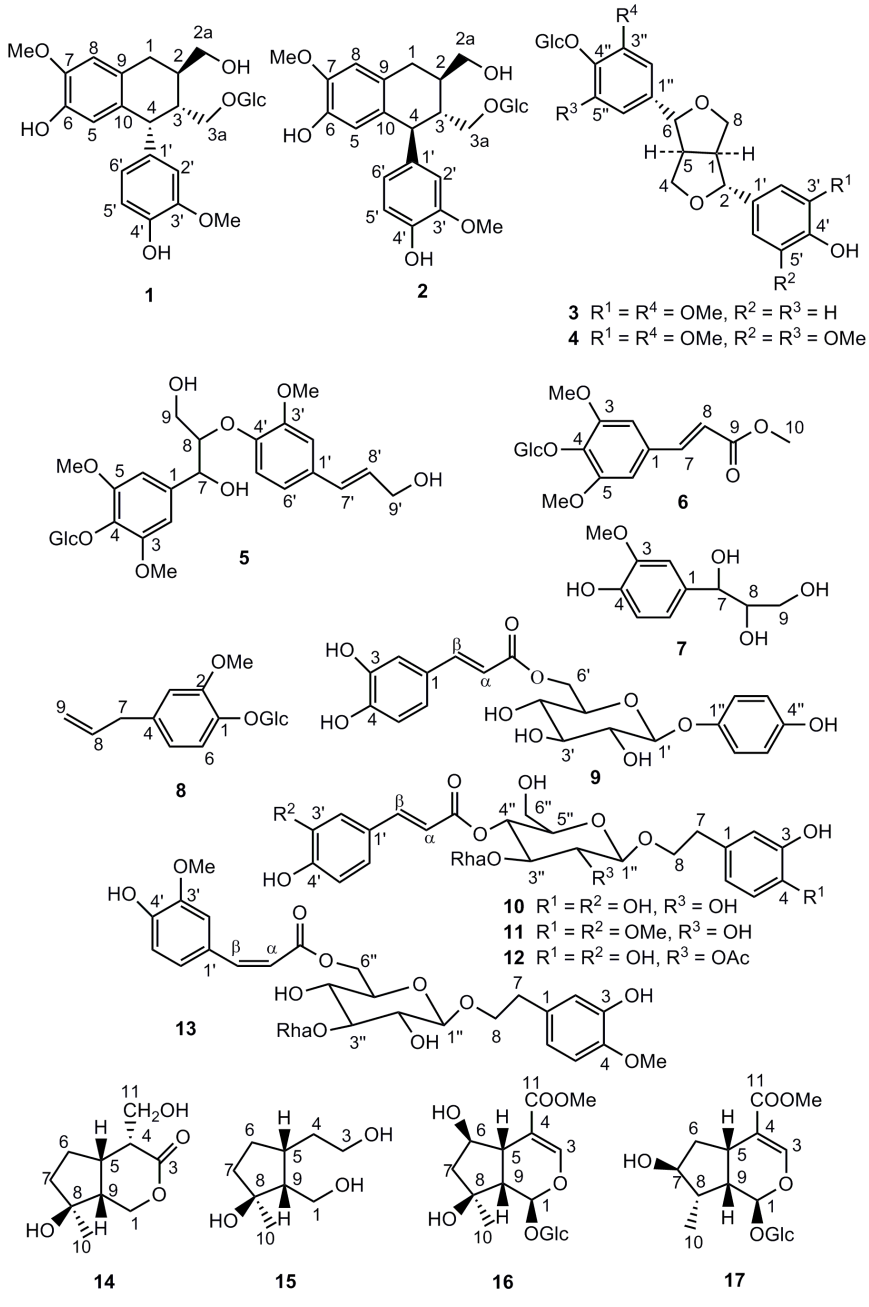


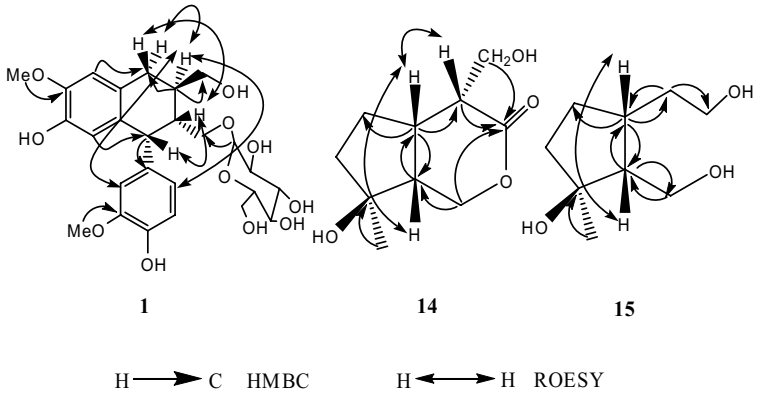
Fig. 1. Structures of compounds **1** – **17**.

1H, J = 16.8, 10.6 Hz, H-1b), 4.25 (1H, d, J = 5.5 Hz, H-4), δ_H = 2.02 (1H, m, H-2) and δ_H = 2.92 (1H, dd, J = 16.8, 5.6 Hz, H-1a), 6.77 (1H, s, H-2′), 6.41 (1H, d, J = 8.1 Hz, H-6′) were observed in the ROESY spectrum (Fig. 2), suggesting that H-3, H-1b and H-4 have the same orientation, and H-2 and H-1a have the same orientation. Moreover, the coupling constant of H-4 (J = 5.5 Hz) agrees with that reported for (–)-4-epi-lyoniresinol 3a-*O*-β-D-glucopyranoside [20], implying that H-4 was in β-orientation. Thus, the structure of **1** was identified as shown in Fig. 1, and the compound was named densispicoside.

Compound **14** was obtained as a colorless solid. The molecular formula of **14** was determined

Table 1. ^{1}H (500 MHz) and ^{13}C NMR (100 MHz) data of compounds **1** and **2** (in CD_3OD, J values in Hz in parentheses).

	1		**2**	
No.	δ_C	δ_H	δ_C	δ_H
1	33.2 (t)	2.92 (dd, 1H, 16.8, 5.6) 2.67 (dd, 1H, 16.8, 10.6)	33.8 (t)	2.80 – 2.83 (m, 2H)
2	35.5 (d)	2.02 (m, 1H)	39.6 (d)	2.07 (m, 1H)
2a	65.2 (t)	3.57 (m, 2H)	65.2 (t)	3.18 – 3.34 (m, overlapped, 2H)
3	42.2 (d)	2.25 (m, 1H)	45.9 (d)	1.85 (t, 1H, 10.2)
3a	71.7 (t)	3.46 (dd, 1H, 9.7, 6.7) 3.80 (overlapped, 1H)	69.6 (t)	3.63 – 3.84 (m, overlapped, 2H)
4	46.7 (d)	4.25 (d, 1H, 5.5)	47.9 (d)	4.06 (d, 1H, 9.9)
5	117.1 (d)	6.34 (s, 1H)	117.4 (d)	6.17 (s, 1H)
6	145.8 (s)		145.8 (s)	
7	147.8 (s)		147.1 (s)	
8	112.4 (d)	6.69 (s, 1H)	112.5 (d)	6.64 (s, 1H)
9	128.6 (s)		129.2 (s)	
10	133.2 (s)		134.4 (s)	
1′	135.8 (s)		138.6 (s)	
2′	115.8 (d)	6.77 (s, 1H)	114.4 (d)	6.78 (s, 1H)
3′	148.1 (s)		148.9 (s)	
4′	145.6 (s)		145.2 (s)	
5′	115.4 (d)	6.62 (d, 1H, 8.1)	116.1 (d)	6.74 (d, 1H, 8.0)
6′	124.3 (d)	6.41 (d, 1H, 8.1)	123.1 (d)	6.63 (overlapped, 1H)
3′-OMe	56.4 (q)	3.76 (s, 3H)	56.4 (q)	3.79 (s, 3H)
7-OMe	56.6 (q)	3.82 (s, 3H)	56.5 (q)	3.79 (s, 3H)
1″	104.6 (d)	4.26 (d, 1H, 8.0)	105.2 (d)	4.11 (d, 1H, 7.7)
2″	75.5 (d)	3.22 – 3.34 (m, 1H)	75.2 (d)	3.18 – 3.84 (m, 1H)
3″	78.2 (d)	3.22 – 3.34 (m, 1H)	78.1 (d)	3.18 – 3.84 (m, 1H)
4″	71.9 (d)	3.22 – 3.34 (m, 1H)	71.7 (d)	3.18 – 3.84 (m, 1H)
5″	78.0 (d)	3.22 – 3.34 (m, 1H)	77.8 (d)	3.18 – 3.84 (m, 1H)
6″	63.0 (t)	3.65 (dd, 1H, 11.6, 4.5) 3.85 (dd, 1H, 11.6, 4.5)	62.8 (t)	3.18 – 3.84 (m, 2H)



1 **14** **15**

H ⟶ C HMBC H ⟷ H ROESY

Fig. 2. Key correlations in the HMBC and ROESY spectra of **1**, **14** and **15**.

to be $C_{10}H_{16}O_4$ by positive ion HR-TOF-MS (m/z = 223.0950, calcd. 223.0946, $[M+23]^+$). The IR spectrum (KBr) showed absorptions for hydroxyl (3426 cm^{-1}) and carbonyl groups (1712 cm^{-1}) and ether functions (1052, 1029 cm^{-1}). The ^{1}H, ^{13}C NMR (DEPT) spectra (see Table 2) of **14** revealed the presence of one methyl, four methylene, three methine, and two quaternary carbon atoms. In the HMBC experiment, long-range correlations were observed between the following protons and carbons: H-1 and C-3, C-9; H-4 and C-3; H-5 and C-4, C-6, C-9; H-9 and C-5; H-10 and C-8; H-11 and C-3 (Fig. 2). On the basis of the above evidence, compound **14** was shown to have a monoterpene structure closely related to that of mussaenin A [5]. The ROESY (Fig. 2) correlation of δ_H = 3.14 (H-5) with δ_H = 2.34 (1H, dd, J = 10.5, 4.7 Hz, H-9) suggested that H-5 and H-9 were both in β-orientation in accordance with those

Table 2. ^{1}H and ^{13}C NMR data of compounds **14** and mussaenin A.

	14[a]		Mussaenin A[b]	
No.	δ_C	δ_H	δ_C	δ_H
1	67.7 (t)	4.36 (dd, 1H, 12.5, 4.8)	68.3 (t)	4.03 (m, 1H)
		4.44 (d, 1H, 12.5)		4.26 (dd, 1H, 11.1, 5.8)
3	177.0 (s)		176.8 (s)	
4	45.3 (d)	2.92 (m, 1H)	46.5 (d)	2.48 (m, 1H)
5	37.3 (d)	3.14 (m, 1H)	37.2 (d)	2.48 (m, 1H)
6	26.8 (t)	1.28 (m, 1H)	30.8 (t)	1.60 (m, 1H)
		1.96 (m, 1H)		2.26 (m, 1H)
7	41.2 (t)	1.50 (m, 1H)	39.7 (t)	1.71 (m, 1H)
		1.67 (m, 1H)		1.79 (m, 1H)
8	81.8 (s)		80.9 (s)	
9	50.0 (d)	2.34 (dd, 1H, 10.5, 4.7)	50.6 (d)	2.26 (m, 1H)
10	24.6 (q)	1.33 (s, 3H)	23.5 (q)	1.24 (s, 3H)
11	60.2 (t)	3.60 (dd, 1H, 11.3, 6.0)	60.8 (t)	3.75 (m, 1H)
		3.95 (dd, 1H, 11.3, 6.0)		3.83 (m, 1H)

[a] ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) in CD_3OD, *J* values in Hz in parentheses; [b] ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) in CD_3OD, *J* values in Hz in parentheses.

of mussaenin A [21]. H-4 was determined to be in β-orientation because a correlation between H-4 and H-5 can be observed in its ROESY spectrum. Thus, the structure of **14** was established as shown in Fig. 1, and the compound was named densispicnin C.

Compound **15** was obtained as a colorless amorphous powder. The positive ion FAB-MS spectrum gave a quasi-molecular ion peak at $m/z = 175$ $[M+1]^+$, and HR-TOF-MS suggested the molecular formula of $C_9H_{18}O_3$ (m/z = 197.1155, calcd. 197.1153, $[M+23]^+$). The IR spectrum (KBr) revealed the presence of hydroxyl (3384 cm^{-1}) and C-O (1052 cm^{-1}) groups. The ^{1}H and ^{13}C NMR (DEPT) spectra of **15** revealed the presence of the following functional groups: one methyl [δ = 1.26, (s, H-10)], five methylenes including two O-bearing ones [δ = 3.59 (m, H-3); 3.64 (m, H-1)], and two methines [δ = 1.90 (m, H-9); 2.48 (m, H-5)]. In the HMBC experiment, long-range correlations were observed between the following protons and carbons: H-5, H-9 and C-1; H-4, H-5 and C-3; H-4, H-6, H-9 and C-5; H-7, H-9, H-10 and C-8; H-1, H-5 and C-9 (Fig. 2). The ROESY correlation of H-5 with H-9 suggested that the configuration of H-5 and H-9 were in accordance with those of natural iridoid compounds. Considering that without the correlation between H-5 with H-10 and with the same chemical shifts as the ones for crescentin IV [22], the configuration of C-8 was comparable with that of crescentin IV. Consequently, the structure of **15** was elucidated as shown in Fig. 1, the compound being designated densispicnin D.

According to the methods described previously [23 – 25], extracts of *P. densispica* in ethanol, petroleum ether, EtOAc, and *n*-BuOH were tested for antitumor activities in cathepsin B, and CDC25 phosphatase inhibition assays (CAT-B, CDC25) and on cancer cell lines (CCLT) *in vitro*. They also were tested for antiosteopororsis, antithrombus and antiglycogen metabolism activities on cathepsin K, plasminogen activator inhibitor 1 and protein phosphatase 1 inhibition assays (CAT-K, PAI-1, PP1) *in vitro*, respectively. Results indicated that the petroleum ether extract of *P. densispica* showed activities in the PAI-1 assay. Extracts of *P. densispica* in ethanol, petroleum ether, EtOAc, *n*-BuOH and water were tested for antifatigue activities in mice. Results indicated that *n*-BuOH and water-dissolved extracts showed antifatigue activities *in vivo*. It is very interesting that verbascoside (**10**) and martynoside (**11**) are the most abundant components of *P. densispica* and were tested for antifatigue activities in mice [26]. Results indicated that two compounds showed antifatigue activities *in vivo*. The bioactivity studies suggest that phenylpropanoid constituents may be the substantial basis for the antifatigue bioactivity of *P. densispica*.

Experimental Section

General

Optical rotations were measured with a Horbia SEAP-300 polarimeter. IR spectra were obtained on a Bio-Rad FTS-135 spectrophotometer with KBr pellets. UV spectra were taken on a Shimadzu 2401PC spectrophotometer. EI, FAB-MS and HR-FAB-MS were recorded on a VG Auto Spec-3000 spectrometer. 1D and 2D NMR spectra were recorded on a Bruker AM-400 and a DRX-500 spectrometer with TMS as internal standard. Column chromatography was performed over silica gel (200 – 300 mesh, Qingdao Marine Chemical Inc., China)

and Sephedex LH-20 (25 – 100 μm, Pharmacia Fine Chemical Co., Ltd., Sweden), respectively.

Plant material

The plant material was collected in Zhong Dian, Yunnan Province of China in August 2004 and identified by Prof. Wang Hong, Kunming Institute of Botany, Chinese Academy of Sciences. The voucher specimen (KUN 0474455) was deposited in the herbarium of Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and isolation

The dried and powdered whole plant material (8.5 kg) of *P. densispica* was extracted three times with 95 % ethanol under reflux. The residue was suspended in water and partitioned with petroleum ether, EtOAc, and *n*-BuOH. The EtOAc portion (52 g) was divided into 3 fractions (Frs. 1 – 3) by silica gel column chromatography eluted with $CHCl_3$-MeOH (100 : 1 to 20 : 1). Fr. 3 was separated by chromatography over reversed-phase C-8 and silica gel to afford compounds **9** (15 mg) and **17** (23 mg). The *n*-BuOH portion (200 g) was divided into 5 fractions (Frs. A – E) by silica gel column chromatography eluted with $CHCl_3$-MeOH (30 : 1 to 6 : 1). Fr. A was subjected to CC over silica gel to afford compounds **3** (100 mg), **4** (21 mg), **6** (3 mg), **7** (7 mg), **8** (35 mg), **14** (45 mg), and **15** (8 mg). Fr. C was purified further by CC Sephadex LH-20 and silica gel to give compounds **11** (40 g) and **13** (10 mg). Compounds **1** (5 mg), **2** (25 mg), **5** (5 mg), and **16** (60 mg) were obtained from Fr. D by HPLC (Zorbax ODS-C18, MeOH-H_2O, 2 : 8). Fr. E was separated by repeated CC on silica gel and Sephadex LH-20 to give **10** (50 g) and **12** (17 mg).

*Densispicoside (**1**).* Colorless amorphous powder. – $[\alpha]_D^{20}$ = −155.7° (*c* = 0.15, CH_3OH). – UV (MeOH): $\lambda(\lg\varepsilon)$ = 206 (4.74) nm. – IR (KBr): ν = 3419, 2926, 1610, 1513, 1430, 1266, 1077, 1033 cm^{-1}. – ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (100 MHz, CD_3OD) data: Table 1. – MS ((–)-FAB): m/z = 521 $[M–1]^-$. – HRMS ((–)-TOF): m/z = 521.2021 (calcd. 521.2022 for $C_{26}H_{33}O_{11}$, $[M–1]^-$).

*(+)-isolarisiresinol 3a-O-β-*D*-glucopyranoside (**2**).* Colorless amorphous powder. – $[\alpha]_D^{21}$ = +38.3° (*c* = 0.40, CH_3OH). – ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (100 MHz, CD_3OD) data: Table 1. – MS ((–)-FAB): m/z = 521 $[M–1]^-$.

*Densispicnin C (**14**).* Colorless solid. – $[\alpha]_D^{21}$ = +127.3° (*c* = 0.36, CH_3OH). – UV (MeOH): $\lambda(\lg\varepsilon)$ = 196 (2.84), 216 (2.97) nm. – IR (KBr): ν = 3426, 2938, 1712, 1052, 1029 cm^{-1}. – ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (100 MHz, CD_3OD) data: Table 2. – MS ((+)-FAB): m/z = 201 $[M+1]^+$. – HRMS ((+)-TOF): m/z = 223.0950 (calcd. 223.0946 for $C_{10}H_{16}O_4Na$, $[M+23]^+$).

Mussaenin A. Colorless solid. – $[\alpha]_D^{21}$ = −15.2° (*c* = 0.06, CH_3OH). – ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data: Table 2. – MS ((+)-FAB): m/z = 201 $[M+1]^+$.

*Densispinin D (**15**).* Colorless amorphous powder. – $[\alpha]_D^{29}$ = +23.7° (*c* = 0.48, CH_3OH). – IR (KBr): ν = 3384, 2939, 1052 cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ_H = 1.26 (3H, s, H-10), 1.37 (1H, m, H-6a), 1.46 (1H, m, H-4a), 1.72 (2H, m, H-7), 1.83 (1H, m, H-4b), 1.88 (1H, m, H-6b), 1.90 (1H, m, H-9), 2.48 (1H, m, H-5), 3.59 (2H, m, H-3), 3.64 (2H, overlapped, H-1). – ^{13}C NMR (100 MHz, CD_3OD): δ_C = 60.2 (t, C-1), 62.4 (t, C-3), 35.0 (t, C-4), 37.1 (d, C-5), 30.1 (t, C-6), 40.7 (t, C-7), 81.6 (s, C-8), 55.7 (d, C-9), 24.9 (q, C-10). – MS ((+)-FAB): m/z (%) = 175 (21) $[M+1]^+$. – HRMS ((+)-TOF): m/z = 197.1155 (calcd. 197.1153 for $C_9H_{18}O_3Na$, $[M+23]^+$).

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