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Short communication

Bioassay-guided isolation of cyclooxygenase-2 inhibitory and antioxidant phenylpropanoid derivatives from the roots of *Dendropanax dentiger*

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ABSTRACT

The root of *Dendropanax dentiger* (Harms) Merr. is a traditional Chinese medicine that has been used to treat inflammation-related diseases with little scientific validation. In this study, a bioassay-guided phytochemical investigation of *D. dentiger* led to the isolation of 19 phenylpropanoid derivatives including one new compound (**1**) and 18 known ones (**2–19**). Their structures were elucidated by NMR and HRMS as well as comparison with literature data. The ability of cyclooxygenase-2 (COX-2) inhibition and antioxidant of all isolated compounds were measured *in vitro*. Chlorogenic acid derivatives (**14–19**) exhibited outstanding COX-2 inhibitory (IC_{50} = 5.1–93.4 μM) and antioxidant (IC_{50} = 13.2–31.9 μM) activities. Moreover, the tight structure-activities relationships were proposed. This is the first report on the COX-2 inhibitory activity of phenylpropanoids and *D. dentiger*.

1. Introduction

Dendropanax Decne. & Planch. a member of the family Araliaceae, comprising 80 species distributed mainly in the tropical America and eastern Asia. Moreover, 16 native species have been found in southwest and southeast of China, and the most prevalent one of these is *D. dentiger* (Harms) Merr., which is widely cultivated in park and commonly used as traditional Chinese medicine (TCM) [1–3]. In TCM, the root of *D. dentiger* (DDR) is a popular traditional herb for inflammatory diseases for centuries [4]. The previous phytochemical studies have found that phenylpropanoids [5,6], polyacetylenes [7], triterpenoids [8] and flavonoids [8] are the main active constituents of *D. dentiger*, which showed potent anti-inflammatory, cytotoxic, antibacterial, antiviral, and antioxidant activities [2,3]. To date, the COX-2 inhibitory activity of *D. dentiger* has not yet been studied so far.

Considering the wide utilization of *D. dentiger* in folk medicine and phytotherapy as well as the recently documented bioactivities of several *Dendropanax* species [3], we aims to isolate the bioactive secondary metabolites in DDR with the COX-2 inhibitory and antioxidant activities. During our ongoing to search for the COX-2 inhibitory and antioxidant activities secondary metabolites from TCMs [9–13], we found that the ethyl acetate (EtOAc) and *n*-butanol (*n*-BuOH) soluble fractions of DDR showed potential COX-2 inhibitory and antioxidant effects. As a result, 19 phenylpropanoids including one new coumarin derivative (**1**) and 18 known compounds (**2–19**) (Fig. 1) were isolated and identified from the EtOAc and *n*-BuOH soluble fractions of DDR. Among them, compounds **2**, **8–10**, **15**, **16**, **18** and **19** were found from the Liliaceae family, while compound **17** from the genus *Dendropanax* for the first time. Described herein are the isolation, structural elucidation, and bioactivity evaluation of all isolated compounds from DDR.

2. Materials and methods

2.1. General experimental procedures

The NMR spectra were recorded on a Bruker AV 600 spectrometer (Fallanden, Switzerland). HR-ESI-MS spectra were measured on a Waters Synapt UPLC G2 TOF mass spectrometer (Manchester, UK). HPLC separation were performed on a Shimadzu LC-6AD system (Kyoto, Japan) with a Gemini preparative HPLC (pre-HPLC) column (5 μm, 21.2 × 250 mm, Phenomenex Inc., CA, USA) and a park ODS-A semi-pre-HPLC column (5 μm, 10 × 250 mm, YMC Co., Ltd., Kyoto, Japan). The silica gel (200–300 mesh) was purchased from Qingdao Haiyang Chemical Group Corporation (Qingdao, China). The octodecyl silica gel (ODS, 60–80 μm) and Sephadex LH-20 were purchased from YMC Co., Ltd. (Tokyo, Japan).

L-ascorbic acid (Vc) was purchased from aladdin (Shanghai, China). 2,2-di-phenyl-1-picrylhydrazyl (DPPH) was purchased from Sigma

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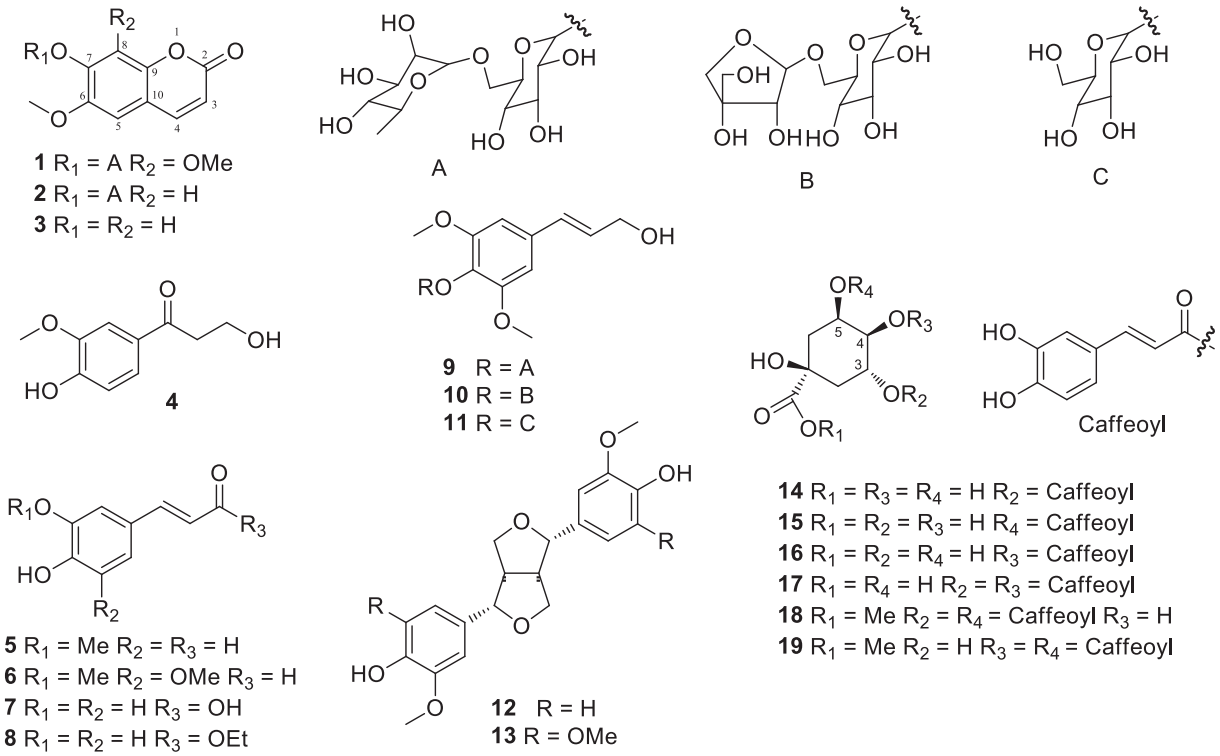

Fig. 1. Chemical structures of compounds **1–19** isolated from DDR.

Corporation (New York, USA), L-cysteine methyl ester and *O*-Tolyl isothiocyanate were purchased from Meilun Biotech. Co. Ltd (Dalian, China), D-glucose, L-glucose, D-rhamnose and L-rhamnose were purchased from Energy Chemical (Shanghai, China). COX-2 inhibitor screening assay kit was purchased from Beyotime Biotechnology (Shanghai, China).

2.2. Plant material

The DDR was harvested from the town of Baidu, Baise City, Guangxi, China, in October 2016. A botanical voucher specimen of this plant (No. DD20161022) was deposited at authors' laboratory, and was identified by one of the authors Ronghua Liu.

2.3. Extraction and isolation

The dried DDR (10.0 kg) were extracted with 95% EtOH (60 L × 3) and subsequently 50% EtOH (60 L × 3) by maceration at room temperature for 7 days. The ethanol crude extract of DDR (1275 g, 12.75%) was suspended in water (2.5 L) and partitioned successively with petroleum ether, EtOAc, and *n*-BuOH to afford four fractions (A-D).

The *n*-BuOH soluble fraction (C, 216.0 g) was subjected to a silica gel chromatographic column (CC) by using CH_2Cl_2/MeOH gradient elution (100:0 → 0:100, v/v) to yield 9 fractions (C1-C9). Fraction C7 (70.0 g) was applied to a silica gel CC eluting with CH_2Cl_2/MeOH (20:1 → 1:1, v/v) to get 5 sub-fractions (C71-C75). Fraction C74 (23.2 g) was isolated by a Sephadex LH-20 CC eluting with 90% MeOH to give 3 sub-fractions (C741-C743). Fraction C742 (4.92 g) was further separated by a silica gel CC (CH_2Cl_2/MeOH = 20:1 → 10:1, v/v) and pre-HPLC to get **1** (12.5 mg), **2** (31.7 mg), **9** (25.4 mg), **10** (6.5 mg) and **11** (3.8 g). The C4 fraction (4.2 g) was subjected to a silica gel CC eluting with a gradient elution (CH_2Cl_2/MeOH = 100:0 → 5:1, v/v) to obtain 8 sub-fractions (C41-C48). Compound **3** (100.0 mg) was obtained with pre-HPLC from C44 (256 mg). Fraction C45 (1.42 g) was separated by an ODS MPLC (10–30% MeOH) and pre-HPLC to yield **13** (120.8 mg) and **8** (45.8 mg). Fraction C75 (40.2 g) was purified by a Sephadex LH-20 CC eluting with 90% MeOH to give 6 sub-fractions (C751-C756). The separation of C753 (4.98 g) following a procedure similar to that used for the fraction C45 gave **14** (364.8 mg), **15** (31.5 mg) and **16** (65.2 mg).

The EtOAc soluble fraction (B, 85.0 g) was subjected to a silica gel CC eluting with a gradient elution (CH_2Cl_2/MeOH = 100:0 → 1:10, v/v) to yield 6 fractions (B1-B6). Fraction B3 (2.16 g) was separated by an ODS MPLC (20–50% MeOH) and pre-HPLC to yield **5** (20.7 mg), **6** (38.2 mg) and **12** (84.2 mg). Fraction B4 (51.0 g) was applied to an ODS MPLC (20–50% MeOH) to get 7 fractions (B41-B47). The separation of B42 (4.0 g) by using a silica gel CC (CH_2Cl_2/MeOH = 30:1 → 5:1, v/v) and pre-HPLC afford **4** (10.6 mg) and **7** (315.6 mg). Fraction B5 (8.1 g) was applied to an ODS MPLC (10–40% MeOH) to get 6 fractions (B51-B56). The separation of B52 (3.2 g) was applied to a silica gel CC (CH_2Cl_2/MeOH = 50:1 → 10:1, v/v) and pre-HPLC to get **17** (17.4 mg), **18** (21.4 mg) and **19** (86.4 mg).

2.4. Acid hydrolysis and HPLC analysis

The absolute configurations of the sugar moieties in compound **1** were described in our previously papers [9,10]. Briefly, Compound **1** (3 mg) was dissolved in 2 mol/L HCl and heated for 2 h at 90 °C. The solvent was evaporated to dryness under vacuum, the residue was dissolved in anhydrous pyridine (1 mL) and then mixed with L-cysteine methyl ester (1 mg), the mixture was heated at 60 °C for one hour. Subsequently, *o*-Tolyl isothiocyanate (5 mL) was added and heated at 60 °C for another one hour. Lastly, the reaction mixture was directly analyzed by HPLC analysis under the following conditions: Phenomenex reversed-phase C18 column (250 × 4.6 mm, 5 μm); detection: 254 nm; mobile phase: CH_3CN-H_2O (25:75, v/v) containing 0.1% formic acid; flow rate: 0.8 mL/min; temperature: 35 °C.

2.5. In vitro COX-2 inhibitory assay

The inhibitory activity of the sample toward COX-2 activity was determined using colorimetric COX inhibitor screening assay kit (no.

S0168) following the manufacturer's instructions, with celecoxib as the positive control.

2.6. DPPH free radical scavenging activity

The DPPH radical scavenging assay was used for the evaluation of antioxidant activity according to the method previously described [9–11]. Briefly, 150 μL of DPPH solution (dissolved 0.2 mM in methanol) was mixed with 50 μL of the sample at different concentrations, then incubated in the dark at 30 °C for 30 min and the absorbance was determined at 517 nm (A_{sample}). The absorbance of a blank (A_{blank}) and control ($A_{control}$) composed of only the sample and DPPH solutions were also determined, respectively. The DPPH radical scavenging activity = [1 - (A_{sample} – A_{blank})/$A_{control}$] × 100%. Vc was used as the positive control in this work.

3. Results and discussion

3.1. Bioactivity-guided isolation

The EtOAc and *n*-BuOH soluble fractions from an ethanol crude extract of DDR showed potential COX-2 inhibitory and antioxidant activities with IC_{50} values of 40.7 ± 3.5 and 28.6 ± 1.9 μg/mL for COX-2 assay, as well as 146.7 ± 8.6 and 206.3 ± 9.2 μg/mL for DPPH assay, respectively, whereas the petroleum ether and aqueous soluble fractions were found to be inactive (Table 1). Therefore, EtOAc and *n*-BuOH fractions were selected for further separation. In this way, 19 phenylpropanoid derivatives (**1**–**19**) were isolated and identified (Fig. 1).

3.2. Spectroscopic data

Dendrocoumarin A **(1)**: white amorphous powder; UV (MeOH) λ_{max}: 207, 257, 294, and 337; ^{1}H and ^{13}C NMR spectroscopic data see Table 2; HR-ESI-MS: *m/z* 531.17083 $[M+H]^+$ (calcd. for $C_{23}H_{31}O_{14}$, 531.17066).

3.3. Structure elucidation

Compound **1** was obtained as white amorphous powder. The HR-ESI-MS with the positive ion at *m/z* 531.17083 $[M+H]^+$ (calcd. 531.17066) indicated that the molecular formula of **1** was $C_{23}H_{30}O_{14}$. The UV spectrum showed the absorption characteristics of coumarin with λ_{max} 207, 257, 294, and 337 nm [14]. The ^{1}H NMR spectrum of **1** (Table 2) showed two methoxy signals at δ_H 3.90 and 3.82 (each, 3H, s, 8/6-CH_3, respectively), two anomeric protons at δ_H 5.07 (1H, d, J = 7.2 Hz, H-1′) and 4.39 (1H, s, H-1″), and three olefinic proton signals at δ_H 7.97 (1H, d, J = 9.5 Hz, H-4), 7.11 (1H, s, H-5) and 6.39 (1H, d, J = 9.5 Hz, H-3). The coupling constant of the two olefinic protons (δ_H 7.97 and 6.39) definitely indicated the double bond with *Z* geometry. Its ^{13}C NMR data (Table 2) exhibited 23 carbon resonances, 12 of which were attributable to two sugar moieties (δ_C 102.4, 100.6, 76.3, 75.7, 74.0, 71.7, 70.5. 70.3, 69.8, 68.2, 66.5 and 17.8), the remaining 11 carbon signals were assigned to one C6-C3 unit (δ_C 159.8, 149.5, 144.4, 142.3, 141.5, 140.3, 114.8, 114.8 and 105.4), and two methoxy groups (δ_C 61.3 and 56.5).

Table 1
Anti-inflammatory and antioxidant activities of four fractions from DDR.[a]

Fractions	COX-2 inhibitory assay	DPPH assay
	IC_{50} (μg/mL)	
Petroleum ether extract	174.6 ± 9.4	> 1000
EtOAc extract	40.7 ± 3.5	146.7 ± 8.6
n-butanol extract	28.6 ± 1.9	206.3 ± 9.2
Water extract	171.9 ± 15.4	496.1 ± 20.5
Vc[b]	–[c]	6.0 ± 0.2
Clecoxib[b]	(22.4 ± 1.4) × 10^{-3}	–[c]

[a] Values are mean ± SD of three experiments, with each data point done in triplicate.
[b] Positive control.
[c] Not tested.

Table 2
^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) for compound **1** in DMSO-d_6 (δ in ppm).

No.	δ_C	δ_H (mult, J in Hz)	No.	δ_C	δ_H (mult, J in Hz)
2	159.8	–[a]	4′	69.8	3.09–3.11 (2H, m)
3	114.8	6.39 (1H, d, 9.5)	5′	75.7	3.18 (1H, m)
4	144.4	7.94 (1H, d, 9.5)	6′	66.5	3.69 (1H, d, 10.9)
5	105.4	7.11 (1H, s)			3.39 (1H, m)
6	149.5	–[a]	1″	100.6	4.39 (1H, s)
7	141.5	–[a]	2″	70.3	3.23–3.26 (4H, m)
8	140.3	–[a]	3″	70.5	
9	142.3	–[a]	4″	71.7	3.09–3.11 (2H, m)
10	114.8	–[a]	5″	68.2	3.23–3.26 (4H, m)
1′	102.4	5.07 (1H, d, 7.2)	6″	17.8	0.98 (3H, d, 6.1)
2′	74.0	3.23–3.26 (4H, m)	6-OMe	56.5	3.82 (3H, s)
3′	76.3	3.23–3.26 (4H, m)	8-OMe	61.3	3.90 (3H, s)

[a] no signal.

The ^{1}H and ^{13}C NMR data of **1** were similar to those of hapoperoside A (compound **2**) [15], except for the presence of an additional methoxy group [δ_H 3.90 (3H, s) and δ_C 61.3, 8-OCH_3] in **1**. Moreover, the additional methoxy group positioned at C-8 was confirmed by the HMBC correlation from 8-OCH_3 to C-8 (δ_C 140.3). Attached positions of the glucose at C-7 and the rhamnose at C-6′ were indicated by HMBC correlations from H-1′ (δ_H 5.07) to C-7 (δ_C 148.8) and from H-1″ (δ_H 4.39) to C-6′ (δ_C 66.5), respectively. Detailed analysis of the ^{1}H–^{1}H COSY, HSQC and HMBC spectra (Fig. 2) further confirmed the structure of **1**. The *β*-anomeric form of glucose was deduced based on the coupling constant ($^3J_{1',2'}$ = 7.2 Hz), whereas the D-configuration (19.5 min) and *α*-L-rhamnose (32.8 min) were determined using HPLC analysis after the acid hydrolysis of **1**, while the peaks of the standard monsaccharide derivatives were recorded at t_R 17.9 (L-glucose), 19.5 (D-glucose) and 32.8 (L-rhamnose) min. On the basis of above evidence, compound **1** was determined to be 6,8-dimethoxy-coumarin-6-*O*-*α*-L-rhamnopyranosyl-(1 → 6)-*β*-D-glucopyranoside, and named Dendrocoumarin A.

Additionally, 18 known compounds were identified as hapoperoside A (**2**) [15], scopoletin (**3**) [16], *β*-hydroxypropiovanillone (**4**) [17], ferulaldehyde (**5**) [18], sinapaldehyde (**6**) [18], caffeic acid (**7**) [19], caffeic acid ethyl ester (**8**) [19], 3,5-dimethoxy-1-(3-hydroxy-propen-1-yl)phenyl-4-*O*-*α*-L-rhamnopyranosyl-(1 → 6)-*β*-D-glucopyranoside (**9**) [20], tinoscorside D (**10**) [21], syringin (**11**) [21], pinoresinol (**12**) [22], syringaresinol (**13**) [23], chlorogenic acid (**14**) [24], neochlorogenic acid (**15**) [25], cryptochlorogenic acid (**16**) [26], 3,4-di-*O*-caffeoylquinic acid (**17**) [26], 3,5-di-*O*-caffeoylquinic acid methyl ester (**18**) [26], and 4,5-di-*O*-caffeoylquinic acid methyl ester (**19**) [26], respectively, based on analysis of their physical and spectroscopic data with those reported earlier. To the best of our knowledge, this is the

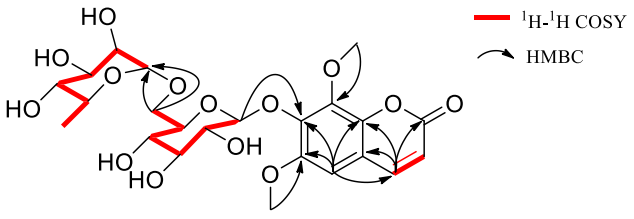

Fig. 2. ^{1}H–^{1}H COSY and key HMBC correlations of compound **1**.

Table 3
Anti-inflammatory and antioxidant activities of compounds **1–19**.[a]

Compound	COX-2 inhibitory assay	DPPH assay	Compound	COX-2 inhibitory assay	DPPH assay
	IC_{50} (μM)			IC_{50} (μM)	
1	58.6 ± 5.6	> 200	**11**	> 100	> 200
2	93.4 ± 8.5	> 200	**12**	28.8 ± 2.1	> 200
3	> 100	> 200	**13**	5.1 ± 0.4	> 200
4	> 100	> 200	**14**	8.1 ± 0.7	31.9 ± 1.6
5	45.6 ± 4.2	> 200	**15**	6.0 ± 0.4	18.0 ± 1.0
6	17.5 ± 1.2	> 200	**16**	5.3 ± 0.3	21.2 ± 1.0
7	11.7 ± 0.9	> 200	**17**	5.5 ± 0.3	13.2 ± 0.8
8	12.1 ± 1.0	> 200	**18**	7.8 ± 0.7	13.2 ± 0.7
9	65.5 ± 5.7	> 200	**19**	9.9 ± 0.9	17.2 ± 0.9
10	69.4 ± 6.1	> 200	Clecoxib[b]	$(34.7 \pm 2.2) \times 10^{-3}$	–[c]
Vc[b]	–[c]	33.9 ± 1.1			

[a] Values are mean ± SD of three experiments, with each data point done in triplicate.
[b] Positive control.
[c] Not tested.

first report on compounds **2**, **8–10**, **15**, **16**, **18** and **19** from the Liliaceae family, and compound **17** from the genus *Dendropanax*.

3.4. COX-2 inhibitory activity

In order to compare the anti-inflammatory activities *in vitro* of the secondary metabolites and to select the most promising bio-constituents, the COX-2 inhibitory activities of all isolated compounds were evaluated at the concentration of 100 μM. Celecoxib was used as the positive control, which was a selective COX-2 inhibitor [9].

As shown in Table 3, compounds **1**, **2**, **5–10** and **12–19** exhibited potential anti-inflammatory effect against COX-2 with IC_{50} values < 100 μM, while **3**, **4** and **11** have no activities with IC_{50} values > 100 μM. It is worth mentioning that compounds **13** and **14–19** exhibited outstanding potency with IC_{50} values less than 10 μM, while **6–8** showed strong activities with IC_{50} values from 11.7 to 17.5 μM. In addition, compounds **5** and **12** displayed obvious inhibitory activities against COX-2 with IC_{50} values of 45.6 ± 4.2 and 28.8 ± 2.1 μM, respectively. Meanwhile, **1**, **2**, **9** and **10** showed moderate effects with IC_{50} values of 58.6–93.4 μM. This is the first reported on the COX-2 inhibitory activities of phenylpropanoids.

Based on the above results, 16 phenylpropanoid derivatives, including **1**, **2**, **5–10** and **12–19,** were identified as the bio-constituents that contributes to the anti-inflammatory effect against COX-2 of DDR. By comparison of the structure type and COX-2 inhibitory activity data of the bioactive secondary metabolites, it was found that the COX-2 inhibitory potency of **13** and chlorogenic acid derivates (**14–19**) were better than the others. In addition, phenylpropanoids showed COX-2 inhibitory activities, which were also reported for the first time.

3.5. Antioxidant activity

The antioxidant activity of all isolated compounds was also assessed by DPPH radical scavenging assay, and the result were summarized in Table 3. The results showed that only chlorogenic acid derivates (**14–19**) exhibited potential antioxidant effects with IC_{50} values in the range of 13.2–31.9 μM, while other phenylpropanoids (**1–13**) have no activities (IC_{50} values > 200 μM). Compounds **14–19** showed significant antioxidant activities with IC_{50} values from 13.2 to 31.9 μM, of which **17** and **18** had the strongest activities with IC_{50} values of 13.2 ± 0.8 and 13.2 ± 0.7 μM, respectively.

Based on the above results, six chlorogenic acid derivates (**14–19**) were identified as the antioxidant secondary metabolites of DDR. The common structural feature of these compounds is that they all have the group of 1,2-diphenols. By comparison, **17–19** with two 1,2-diphenols (four phenolic hydroxyl groups) had stronger antioxidant capacity than **14–16** with one 1,2-diphenol, while compounds **1–13** with no or one phenolic hydroxyl group were inactive. Therefore, the number and position of phenolic hydroxyl groups of compounds are directly related to their *in vitro* antioxidant effects, which were consistent with reported papers [9,27].

4. Conclusion

In this work, 19 phenylpropanoids (**1–19**) including one new coumarin derivative (**1**) were isolated and identified from DDR through bioactivity-guided separation. All isolated compounds were evaluated for their COX-2 inhibitory and antioxidant activities *in vitro*, and the tight structure-activities relationships were proposed. Moreover, 6 chlorogenic acid derivatives (**14–19**) exhibited outstanding COX-2 inhibitory (IC_{50} = 5.1–93.4 μM) and antioxidant (IC_{50} = 13.2–31.9 μM) activities. This is the first report on the COX-2 inhibitory activity of phenylpropanoids and *D. dentiger*. Our findings suggested that the anti-inflammatory and antioxidant effects of DDR were partly attributed to these phenylpropanoids especially chlorogenic acid derivates, and support the claim as sources of important folk medicine in TCM used to treat inflammation-related diseases for centuries.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.104211.

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