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Two New Flavonoids from the Nuts of *Areca catechu*

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Abstract: Two new flavonoids, calquiquelignan M (**1**), calquiquelignan N (**2**), along with nine known compounds (**3–11**), were isolated from the nuts of *Areca catechu* (Palmae). The new structures, including absolute configurations, were established by a combination of spectroscopic data and electronic circular dichroism (ECD) calculation. The known compounds were identified by comparing their spectroscopic data with reported in the literature. The flavonoids compounds (**1–8**) were evaluated for their cytotoxicity activities against three human cancer cell lines. Compounds **1** and **2** exhibited a moderate cytotoxic activity against HepG2 cell lines with IC₅₀ values of 49.8 and 53.6 μM, respectively.

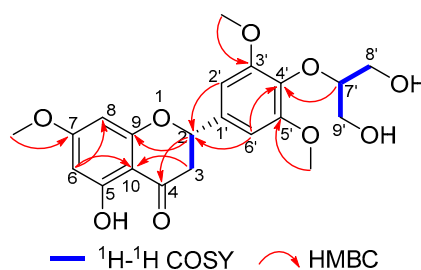
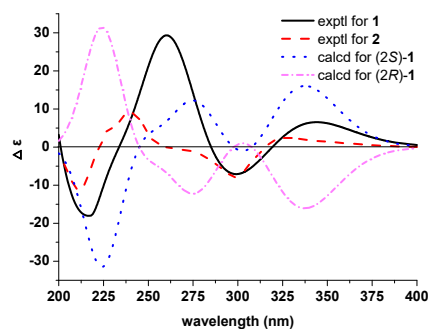
Keywords: *Areca catechu*; flavonoids; absolute configuration; cytotoxicity

1. Introduction

Areca nut is obtained from the fruit of the *Areca catechu* (Palmae), which is widely distributed in southeast Asia and southern China [1]. Areca nuts are regarded as a traditional Chinese medicine usually used for the treatment of indigestion, liver disorders, and also used as a vermifuge [2,3]. Previous pharmacological studies of areca nuts have demonstrated antibacterial, antioxidant, anti-inflammatory, antifungal, and anthelmintic activities [4,5]. In a search for novel and bioactive constituents from Chinese herbal medicines [6–10], our group had reported three new areca alkaloids from the nuts of *A. catechu* [11]. In our continuing investigation, two new flavonoids calquiquelignan M (**1**), calquiquelignan N (**2**), and nine known compounds naringenin (**3**) [12], dihydrotricin (**4**) [13], sinasetin (**5**) [14], nobiletin (**6**) [15], 8-demethyleucalyptin (**7**) [16], eucalyptin (**8**) [16], (+)-isolariciresinol (**9**) [17], rhapontigenin (**10**) [18], glyceryl-2-vanillic acid methyl ester (**11**) [19], were isolated from the same plant parts as shown in Figure 1. The new structures, including absolute configurations, were elucidated by spectroscopic data and electronic circular dichroism (ECD) calculation, and the known ones were identified by comparison with data in the literature. Herein, we report the isolation, structure elucidation, and cytotoxic activities of these compounds.

Table 1. ^1H - and ^{13}C -NMR data of **1** and **2** (δ in ppm, J in Hz).

Position	1 ^a		2 ^b	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}
2	5.36 dd (13.0, 3.0)	79.4	5.45 dd (11.0, 6.0)	80.7
3	α 3.05 dd (17.0, 13.0)	43.8	3.18 dd (16.5, 11.0)	44.4
	β 2.82 dd (17.0, 3.0)		2.81 dd (16.5, 6.0)	
4	-	195.5	-	197.8
5	-	164.4	-	165.3
6	6.08 s	95.4	6.08 s	95.9
7	-	168.2	-	169.6
8	6.09 s	94.6	6.12 s	95.1
9	-	162.6	-	164.4
10	-	103.2	-	104.1
1'	-	135.0	-	136.5
2'/6'	6.71 s	103.4	6.87 s	104.9
3'/5'	-	153.6	-	154.4
4'	-	135.7	-	137.4
7'	4.08 m	85.0	4.14 m	88.9
8'	3.85 d (3.4)	62.7	5.02 d (6.7)	74.5
9'	α 3.77 d (3.4)	62.7	3.79 m	61.8
	β		3.37 m	
1''	-	-	-	133.5
2''	-	-	7.03 s	111.7
3''	-	-	-	148.7
4''	-	-	-	147.2
5''	-	-	6.77 d (8.0)	115.8
6''	-	-	6.89 d (8.0)	120.8
7-OCH ₃	3.82 s	55.9	3.85 s	56.4
3'-OCH ₃	3.91 s	56.5	3.89 s	56.8
5'-OCH ₃	3.91 s	56.5	3.89 s	56.8
3''-OCH ₃	-	-	3.84 s	56.3

^a Measured in CDCl₃. ^b Measured in CD₃OD.**Figure 2.** ^1H - ^1H COSY and key HMBC correlations of **1**.**Figure 3.** Experimental electronic circular dichroism (ECD) spectra for **1** and **2**; and calculated for **1**.

Calquiquelignan N (**2**) was obtained as a yellow powder, possessed a molecular formula $C_{28}H_{30}O_{11}$ as established by its HR-ESI-MS at m/z 565.1685 $[M + Na]^+$ (calcd for $C_{28}H_{30}O_{11}Na$, 565.1680). The IR absorption revealed the presence of hydroxyl (3443 cm^{-1}), carbonyl (1651 cm^{-1}) groups, as well as an aromatic ring (1511 and 1429 cm^{-1}). The UV spectrum showed the characteristic absorption maxima at 287, 230, and 208 nm. The $^1\text{H-NMR}$ spectrum indicated the presence of seven aromatic protons [δ_{H} 7.03 (1H, s, H-2''), 6.89 (1H, d, $J = 8.0$ Hz, H-6''), 6.87 (2H, s, H-2'/6'), 6.77 (1H, d, $J = 8.0$ Hz, H-5''), 6.12 (1H, s, H-8), 6.08 (1H, s, H-6)]; three methines [δ_{H} 5.45 (1H, dd, $J = 11.0, 6.0$ Hz, H-2), 5.02 (1H, d, $J = 6.7$ Hz, H-8'), 4.14 (1H, m, H-7')]; two methylenes [δ_{H} 3.18 (1H, dd, $J = 16.5, 11.0$, H-3 α), 2.81 (1H, dd, $J = 16.5, 6.0$, H-3 β), 3.79 (1H, m, H-9'a), 3.37 (1H, m, H-9'b)], and four methoxys [δ_{H} 3.89 (6H, s), 3.85 (3H, s), 3.84 (3H, s)]. The $^{13}\text{C-NMR}$ spectrum displayed 28 carbon signals, including a chelated phenolic ketone carbon, eighteen olefinic carbons, three methines, two methylenes, and four methoxys (Table 1). The above-NMR of **2** resembled those of **1**, except for the absence of a methylene, and the present of a 1'',3'',4''-trisubstitution phenyl ring and a methine at (δ_{C} 74.5). The signal at δ_{C} 74.5 was assigned to C-8' indicated the 1'',3'',4''-trisubstitution phenyl ring substituted there, which was supported by the HMBC correlations between H-8' and C-2''/C-6''. Furthermore, the HMBC correlations between H-7' and C-4' confirmed the C-4'-O-C-7' bond existence, and correlations between methoxy (δ_{H} 3.84) and C-3'', led to the methoxy substitution position at C-3'' (Figure 4). Thus, the planar structure of **2** was determined, as shown in Figure 4.

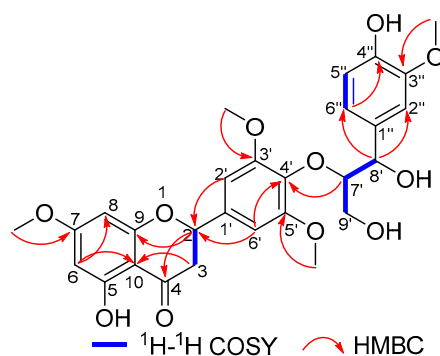


Figure 4. $^1\text{H-}^1\text{H}$ COSY and key HMBC correlations of **2**.

Generally, adjacent protons of the *erythro* type have been reported to have smaller coupling constants (2.8–5.6 Hz) than those of the *threo* type (6.0–8.6 Hz) in different *d*-solvents [21–23]. Likewise, compound **2** was identified as a *threo*-configuration due to the 6.7 Hz coupling constants between H-7' and H-8' in CD_3OD . Furthermore, the agreement of the ECD spectrum of **2** with those of **1** allowed the absolute configuration of **2** to be determined as 2*S* (Figure 3).

The pharmacological study of flavonoids and their derivatives showed that they possess cytotoxic activity [24]. Thus, the flavonoid compounds (**1**–**8**) were tested for their cytotoxic activity against three human cancer cells MCF-7, HepG2, and A-549 using MTT assay. Compounds **1** and **2** exhibited a moderate cytotoxic activity against HepG2 cell lines with IC_{50} values of 49.8 and 53.6 μM , respectively (Table 2).

Table 2. Cytotoxicity of compounds **1**–**8** (IC_{50} , μM).

Compound	MCF-7	A-549	HepG2
1	>100	>100	49.8
2	>100	>100	53.6
3	>100	>100	>100
4	>100	>100	>100
5	>100	>100	>100
6	>100	>100	89.6
7	>100	>100	>100
8	>100	>100	>100
cisplatin	19.8	15.3	17.6

3. Materials and Methods

3.1. General Experimental Procedures

Optical rotation was carried out using a Jasco P-1020 digital polarimeter (JASCO, Tokyo, Japan). UV spectra were obtained on a Jasco V-550 UV/VIS spectrometer (JASCO, Tokyo, Japan), and IR spectra on a Jasco FT/IR-480 plus infrared spectrometer (JASCO, Tokyo, Japan) with KBr discs. HR-ESI-MS data were detected on an Agilent 6210 ESI/TOF mass spectrometer (Agilent, Palo Alto, CA, USA). NMR spectra were recorded on Bruker AV-500 spectrometer (Bruker, Karlsruhe, Germany). Column chromatography (CC) was performed on silica gel (80~100 and 200~300 mesh; Qingdao Marine Chemical Inc., Qingdao, China), ODS (YMC, Kyoto, Japan) and Sephadex LH-20 (Pharmacia Biotech AB). Preparative HPLC was carried out on an Agilent 1260 system (G1311 pump and G1315D photodiode array detector) with a C₁₈ reversed-phase column (20 × 250 mm, 5 μm, Shiseido Fine Chemicals Ltd., Osaka, Japan).

3.2. Plant Material

The areca nuts were collected in Sanya, Hainan province, P. R. China, in October 2014, and identified by Professor Guang-Xiong Zhou (College of Pharmacy, Jinan University). A voucher specimen (No. CP2014101403) was deposited at the herbarium of the College of Pharmacy, Jinan University, Guangzhou, P. R. China.

3.3. Extraction and Isolation

The air-dried and powdered areca nuts (30.0 kg) were extracted at room temperature with 95% EtOH to afford a residue (1.1 kg), which was then suspended in H₂O and treated with 0.5% hydrochloric acid to adjust the pH to 2 to 3. After extraction with CHCl₃, the CHCl₃ extract (60.0 g) was subjected to silica gel column chromatography and eluted with CHCl₃–CH₃OH (100:0 → 0:100) to afford 8 fractions (Fr. A–H). Fr. D (2.8 g) was chromatographed on Sephadex LH-20 (CHCl₃–CH₃OH, 1:1) and HPLC (CH₃OH–H₂O, 35:65) to afford **1** (7.2 mg, *t*_R 14.3 min), **2** (6.8 mg, *t*_R 28.7 min), **3** (10.4 mg, *t*_R 37.6 min). Fr. E (5.9 g) was separated by Sephadex LH-20 (CHCl₃–CH₃OH, 1:1) and further HPLC (CH₃OH–H₂O, 50:50) to afford **9** (35.8 mg, *t*_R 17.8 min) and **11** (26.3 mg, *t*_R 29.8 min). Fr. F (2.3 g) was subjected to ODS CC (CH₃OH–H₂O, 1:9 → 7:3) and HPLC (CH₃OH–H₂O, 40:60) to yield **4** (9.2 mg, *t*_R 40.4 min), **7** (6.7 mg, *t*_R 25.8 min), **8** (8.3 g, *t*_R 33.8 min), **10** (12.3 g, *t*_R 19.6 min). Fr. G (1.9 g) was separated by Sephadex LH-20 (CHCl₃–CH₃OH, 1:1) and further HPLC (CH₃OH–H₂O, 40:60) to afford **5** (12.2 mg, *t*_R 24.1 min) and **6** (10.5 mg, *t*_R 35.8 min).

Calquiquelignan M (**1**): yellow powder; $[\alpha]_D^{25} - 8.9$ (*c* 0.36, CH₃OH); UV (CH₃OH) λ_{\max} (log ϵ): 208 (4.14), 287 (3.88) nm; CD (CH₃OH, $\Delta\epsilon$) λ_{\max} : 342 (+6.6), 299 (−7.0), 260 (+29.3), 216 (−18.2) nm; IR (KBr) ν_{\max} 3477, 1660, 1621, 1535, 1450, 1304, 1158, 1114 cm^{−1}; ¹H- and ¹³C-NMR spectral data, see Table 1; HR-ESI-MS: *m/z* [M + Na]⁺, calcd for C₂₁H₂₄O₉Na: 443.1313, found: 443.1310.

Calquiquelignan N (**2**): yellow powder; $[\alpha]_D^{25} - 13.5$ (*c* 0.47, CH₃OH); UV (CH₃OH) λ_{\max} (log ϵ): 208 (4.45), 230 (4.02), 287 (4.05) nm; CD (CH₃OH, $\Delta\epsilon$) λ_{\max} : 324 (+2.5), 299 (−7.9), 250 (+3.4), 211 (−11.3) nm; IR (KBr) ν_{\max} 3443, 1651, 1511, 1429, 1362, 1032, 826 cm^{−1}; ¹H- and ¹³C-NMR spectral data, see Table 1; HR-ESI-MS: *m/z* [M + Na]⁺ calcd for C₂₈H₃₀O₁₁Na: 565.1680, found: 565.1685.

¹H- and ¹³C-NMR spectra of these compounds are available in the Supplementary Materials.

3.4. Computational Calculation

Conformational searches were performed in the Sybyl 8.1 software by using the MMFF94S molecular force field, which afforded 12 conformers for **1**, with an energy cutoff of 10 kcal/mol. The ECD calculation for the optimized conformers was carried out using time-dependent DFT (TDDFT) methods at the B3LYP/6-31+G(d) level in the gas phase by using Gaussian 09 software. The overall ECD curves of **1** were weighted by Boltzmann distribution of each conformer (with a half-bandwidth

of 0.3 eV). The calculated ECD spectra of **1** were subsequently compared with the experimental ones. The ECD curves were produced by SpecDis 1.6 software (University of Wuerzburg, Bavaria, Germany).

3.5. Cytotoxicity Assay

The MTT assay for the determination of the cytotoxicity was performed as described previously [25]. Briefly, cancer cells were plated into 96-well plates. After 48 h of preculture, the cells were treated with compounds at various concentrations for 72 h and then stained with MTT. Absorbance at 570 nm was measured on a microplate reader.

4. Conclusions

In summary, we isolated two new flavonoids, calquiquelignan M and N (**1–2**) and nine known compounds naringenin (**3**), dihydrotricin (**4**), sinesetin (**5**), nobiletin (**6**), 8-demethyleucalyptin (**7**), eucalyptin (**8**), (+)-isolariciresinol (**9**), rhapontigenin (**10**), glyceryl-2-vanillic acid methyl ester (**11**) from the nuts of *A. catechu*. The new compounds were elucidated by spectroscopic analyses, and computational calculation, and the known ones were identified by comparing their spectroscopic data with reported in the literature. Moreover, all of the flavonoids (**1–8**) were evaluated for their cytotoxicity activities against three human cancer cell lines. Compounds **1** and **2** showed moderate cytotoxicity against HepG2 cell lines with IC₅₀ values of 49.8 and 53.6 µM, respectively.

Supplementary Materials: The following are available online, Computational data of **1**. Cytotoxicity assay. Figures S1–S9: HRESIMS, UV, IR, 1D, and 2D-NMR spectra of compound **1**. Figures S10–S17: HRESIMS, UV, IR, 1D, and 2D-NMR spectra of compound **2**.

Author Contributions: M.Y., Y.A., and J.X. isolated and identified the structure of the compounds. N.Y. and D.Z. carried out the cytotoxicity assay. J.Z. and X.Z. designed and supervised the study, and wrote and revised the manuscript. W.Y. revised the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds 1–11 are available from the authors.



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