Constituents of *Vittaria anguste-elongata* and Their Biological Activities

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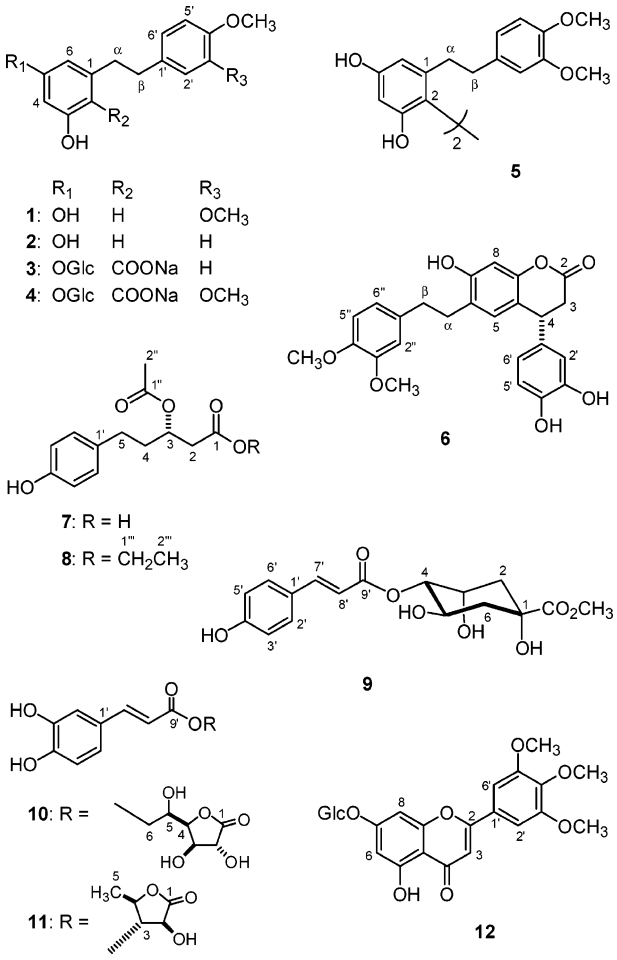
Twelve new compounds, vittarin-A (**1**), -B (**2**), -C (**3**), -D (**4**), -E (**5**), -F (**6**), 3-*O*-acetylniduloic acid (**7**), ethyl 3-*O*-acetylniduloate (**8**), methyl 4-*O*-coumaroylquinate (**9**), vittarilide-A (**10**), and -B (**11**), and vittariflavone (**12**), as well as 20 known compounds have been isolated from the whole plant of *Vittaria anguste-elongata*. The structures of these compounds were determined by spectroscopic and chemical transformation methods. 5,7-Dihydroxy-3′,4′,5′-trimethoxyflavone (**18**) displayed moderate cytotoxicity against human lung carcinoma and central nervous system carcinoma cell lines with inhibition of 89 and 61% at a concentration of 58 μM, respectively. Vittarilide-A (**10**) and -B (**11**) and ethyl 4-*O*-caffeoylquinate (**14**) exhibited moderate DPPH radical scavenging activity with IC_{50} values of 91, 290, and 234 μM, respectively.

Vittaria anguste-elongata Hayata, family Vittariaceae, is a linear grass-like fern indigenous to Taiwan. Fronds of *V. anguste-elongata* are nearly sessile and winged to base, and tufted. It is found mainly growing on trees or moss covered rocks in low altitude forests.[1] In the course of our screening of natural product extracts of medicinal plant origin that exhibit selective cell growth inhibitory and/or cytotoxic activity against human cancer cell lines, we identified a crude methanol extract of the whole plant of *V. anguste-elongata* with significant cytotoxicity against gastric and nasopharynx carcinoma cell lines. The isolation, structure elucidation, and biological activity of 12 new and 20 known compounds from the whole plant of *V. anguste-elongata* are described in this report.

Results and Discussion

The MeOH extract of *V. anguste-elongata* was suspended in H_2O and defatted with hexane. The aqueous solution was partitioned with $CHCl_3$ and EtOAc, successively. The $CHCl_3$- and EtOAc-soluble fractions were individually separated by silica gel column chromatography to afford 32 compounds, including 12 new compounds—four bibenzyls, vittarin-A to -D (**1**−**4**); one bisbibenzyl, vittarin-E (**5**); one dihydrocoumarin, vittarin-F (**6**); five benzenoids, 3-*O*-acetylniduloic acid (**7**), ethyl 3-*O*-acetylniduloate (**8**), methyl 4-*O*-coumaroylquinate (**9**), vittarilide-A (**10**) and -B (**11**); one flavone, vittariflavone (**12**)—and 20 known compounds: methyl 4-*O*-caffeoylquinate (**13**),[2] ethyl 4-*O*-caffeoylquinate (**14**),[3] methyl 5-*O*-caffeoylquinate (**15**),[4] apigenin (**16**),[5] vitexin (**17**),[6] 5,7-dihydroxy-3′,4′,5′-trimethoxyflavone (**18**),[7] amentoflavone (**19**),[8] *trans-p*-coumaric acid (**20**),[9] methyl *trans-p*-coumarate (**21**),[10] methyl caffeate (**22**),[11] ferulic acid (**23**),[9] *p*-cresol (**24**),[12] 4-hydroxybenzaldehyde (**25**),[6] 4-hydroxybenzoic acid (**26**),[9] methyl 4-hydroxybenzoate (**27**),[13] protocatechualdehyde (**28**),[14] protocatechuic acid (**29**),[6] methyl protocatechuate (**30**),[6] vanillin (**31**),[6] and vanillic acid (**32**).[9]

Vittarin-A (**1**) was isolated as white crystals. The molecular ion at *m/z* 274.1206 in the HREIMS corresponded to the molecular formula $C_{16}H_{18}O_4$. The UV absorption maxima at 230 and 280 nm indicated the existence of an aromatic system. The IR spectrum showed absorptions for a hydroxyl functionality at 3390 cm^{-1} and an aromatic group at 1601 and 1515 cm^{-1}. In the aromatic region of the ^1H NMR spectrum, two sets of aromatic signals, at δ 6.19 (1H, t, J = 2.0 Hz, H-4), 6.23 (2H, d, J = 2.0 Hz, H-2 and -6) and at δ 6.65 (1H, d, J = 1.6 Hz, H-2′), 6.71 (1H, dd, J = 8.1, 1.6 Hz, H-6′), 6.79 (1H, d, J = 8.1 Hz, H-5′), were assigned by COSY to a symmetrical 1,3,5-trisubstituted and a 1,3,4-trisubstituted benzene ring, respectively. In the aliphatic region, two multiplets at δ 2.78 and 2.83 (each 2H) were attributed to a $-CH_2CH_2-$ group. The ^3J correlations of the former signal with C-1′, -2, and -6 and the latter with C-1, -2′, and -6′ in the HMBC spectrum



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indicated a bibenzyl skeleton for **1**. The NOEs of two *O*-methyl signals at δ 3.84 and 3.86 with H-2′ and H-5′, respectively, and two hydroxyl groups at δ 4.79 with H-2, H-4, and H-6 indicated that two hydroxyls were attached to a symmetrical benzene ring and two *O*-methyl groups on the other ring. Consequently, a 3,5-dihydroxy-3′,4′-dimethoxybibenzyl was deduced for the structure of **1** and named vittarin-A.

Vittarin-B (**2**), obtained as white crystals, had a molecular formula of $C_{15}H_{16}O_3$, which was determined by HREIMS. As shown in the Experimental Section, the UV, IR, and ^{1}H and ^{13}C NMR spectroscopic features of **2** were similar to those of **1**, implying that **2** was also a bibenzyl derivative. The ^{1}H NMR spectrum showed that **2** contained a symmetrical *p*-methoxyphenyl moiety due to the proton signals at δ 3.79 (3H, s, 4′-OCH_3), 6.82 (2H, d, J = 8.4 Hz, H-3′ and -5′), and 7.08 (2H, d, J = 8.4 Hz, H-2′ and -6′) instead of a 1,3,4-trisubstituted benzene unit in **1**. Thus, vittarin-B (**2**) is 3,5-dihydroxy-4′-methoxybibenzyl. Although **2** has been synthesized by Orsini et al.,[15] this represents its first isolation from a natural source.

Vittarin-C (**3**), obtained as yellowish syrup, was also determined to be a bibenzyl derivative by comparison of the spectroscopic data with those of **1** and **2**. The ^{1}H NMR spectrum of **3** showed the presence of a $-CH_2CH_2-$ group [δ 3.05 (2H, t, J = 8.0 Hz, H-β) and 3.69 (2H, t, J = 8.0 Hz, H-α)], one 1,4-disubstituted aromatic ring [δ 6.89 (2H, d, J = 8.2 Hz, H-3′ and -5′), 7.35 (2H, d, J = 8.2 Hz, H-2′ and -6′)], and a 1,2,3,5-tetrasubstituted aromatic ring [δ 6.75 and 7.06 (each 1H, d, J = 2.1 Hz)]. The 1,2,3,5-tetrasubstituted aromatic ring contained two *m*-coupled protons, which were assigned to H-6 and H-4, respectively, since only the latter signal showed NOE and HMBC correlations with H-α and C-α, respectively. An *O*-methyl group at δ 3.65 (3H, s) was connected to C-4′ of a 1,4-disubstituted aromatic ring, as it showed HMBC correlation with C-4′ and NOEs with H-3′ and -5′. A characteristic doublet at δ 5.66 (1H, d, J = 7.1 Hz) with a large coupling constant was ascribed to the anomeric proton of the β-glucopyranosyl unit. Accordingly, the ^{13}C NMR spectrum had signals of a glucose moiety at δ 62.3, 71.2, 75.0, 78.5, 78.8, and 101.7. The anomeric proton H-1″ exhibited NOEs with H-4 and -6 as well as HMBC with C-5, indicating the attachment of glucose to C-5. A carbon signal at δ 177.7 along with a strong IR absorption at 1589 cm^{-1} were indicative of a carboxylate ion, which was placed on C-2 on the basis of HMBC correlations between H-4, H-6 and C-2. Compound **3** was acidified with a hot 4% HCl solution, and the reaction mixture was passed through a Sephadex LH-20 column using deionized H_2O followed by MeOH. The H_2O eluent contained a sodium ion by atomic absorption. In addition, the MeOH eluent gave compound **2**, which was formed from **3** by the elimination of glucose and CO_2.[16] Therefore, the sodium salt of 5-glucosyloxy-3-hydroxy-4′-methoxybibenzyl-2-carboxylic acid was proposed for the structure of vittarin-C (**3**). This compound indeed showed a pseudomolecular ion at *m/z* 473.1425 $[M + H]^+$ for a molecular formula of $C_{22}H_{25}O_{10}Na$.

Vittarin-D (**4**) exhibited a pseudomolecular ion at *m/z* 503.1527 $[M + H]^+$ in the HRFABMS for a molecular formula $C_{23}H_{27}O_{11}Na$. The ^{1}H and ^{13}C NMR spectra of **4** were almost superimposable on those of **3** except for the absence of one proton and the presence of one prominent signal for an *O*-methyl group at δ 3.75, which showed a NOE cross-peak with H-2′ at δ 7.24. Interpretation of the 2D NMR data of **4** led to the assignment of the structure of vittarin-D (**4**) as the sodium salt of 5-glucosyloxy-3-hydroxy-3′,4′-dimethoxybibenzyl-2-carboxylic acid.

Vittarin-E (**5**), obtained as white crystals, had a molecular formula $C_{32}H_{34}O_8$ from its pseudomolecular ion at *m/z* 569.2149 for $[M + Na]^+$. The ^{13}C NMR spectrum exhibited 16 ^{13}C signals, indicating that the structure of **5** was symmetric. The IR spectrum showed the hydroxyl absorption at 3374 cm^{-1}. The ^{1}H NMR spectrum displayed the typical signals of a $-CH_2CH_2-$ at δ 2.79 and 3.18 (t, J = 7.4 Hz), an aromatic ABX system at δ 6.74 (dd, J = 8.0, 2.1 Hz), 6.76 (d, J = 2.1 Hz), and 6.82 (d, J = 8.0 Hz), an aromatic ring with two *m*-coupled doublets at δ 6.11 and 6.15 (J = 2.5 Hz), and two *O*-methyl singlets at δ 3.79. These data were very similar to those of **1** except for the disappearance of the H-2 resonance. HMBC and NOESY analysis indicated that compound **5** comprised two 2-substituted 3,5-dihydroxy-3′,4′-dimethoxybibenzyl moieties. Thus, the bisbibenzyl structure of vittarin-E was established as **5**.

Vittarin-F (**6**), an optically active compound with $[\alpha]_D$ = −5.4°, was isolated as a white amorphous powder. The HREIMS gave the molecular formula $C_{25}H_{24}O_7$. The IR spectrum showed hydroxyl and carbonyl absorptions at 3386 and 1701 cm^{-1}. From the ^{1}H NMR, COSY, and HMQC spectra, three mutually coupled protons at δ 2.76 (dd, J = 15.5 and 2.2 Hz, H-3a), 2.98 (dd, J = 15.5, 6.5 Hz, H-3b), and 4.34 (dd, J = 6.5, 2.2 Hz, H-4), indicative of a $-CH_2$-CH− fragment, and two aromatic singlets at δ 6.46 and 6.59 were attributed to a 4,6,7-trisubstituted dihydrocoumarin unit. This assignment was supported by the ^3J correlation of H-4 with C-2, -5, and -9 in the HMBC spectrum. Furthermore, H-4 also showed HMBC connectivities with C-2′ and -6′, which belonged to an aromatic ring containing two hydroxyls on C-3′ and -4′ [δ 6.47 (1H, dd, J = 8.1, 1.9 Hz, H-6′), 6.54 (1H, d, J = 1.9 Hz, H-2′), and 6.74 (1H, d, J = 8.1 Hz, H-5′)]. Another aromatic ring [δ 6.60 (1H, dd, J = 7.9, 2.1 Hz, H-6″), 6.62 (1H, d, J = 2.1 Hz, H-2″), 6.79 (1H, d, J = 7.9 Hz, H-5″)] with two *O*-methyl substituents (δ 3.73 and 3.74) bearing a $-CH_2$-CH_2- group [δ 2.56 (t, J = 7.8 Hz, H-β), 2.73 (t, J = 7.8 Hz, H-α)] was connected to C-6 of the 4-aryldihydrocoumarin by the ^3J HMBC correlation between H-β and C-6. The ^{13}C signal of C-7 at δ 158.3 indicated a hydroxyl was attached to it. The foregoing spectroscopic analysis elucidated the structure of 4-(3′,4′-dihydroxyphenyl)-6-(3″,4″-dimethoxyphenylethyl)-7-hydroxydihydrocoumarin for vittarin-F (**6**). The absolute configuration at C-4 was determined by comparison of the specific rotation with that of (*S*)-4-(3′-isopropylphenyl)-7-methoxydihydrocoumarin ($[\alpha]_D$ = +25.4°), which was synthesized by McGuire et al.[17] Therefore, the negative optical rotation of **6** indicated an *R* configuration at C-4.

3-*O*-Acetylniduloic acid (**7**) was an optically active colorless syrup, $[\alpha]_D$ = −47.6°. Its HREIMS data inferred the molecular formula $C_{13}H_{16}O_5$. The ^{1}H NMR spectrum exhibited signals for aromatic protons in a *p*-substituted phenyl ring at 6.67 and 6.99 (each 2H, d, J = 8.3 Hz) with an electron-donating hydroxyl group at C-4′. Analysis on the basis of the ^{1}H and ^{13}C NMR data combined with COSY, HMQC, and HMBC spectra allowed the assignment of a $-CH_2CH_2CHCH_2-$ fragment due to the signals at δ 1.89 (2H, m, H-4), 2.40 and 2.51 (each 1H, dd, J = 14.2, 6.5 Hz, H-2), 2.56 (2H, m, H-5), and 5.26 (1H, quintet, J = 6.5 Hz, H-3). A carboxylic [δ_C 178.6 (C-1)] and an acetoxy group [δ_H 1.99 (3H, s, H-2″); δ_C 21.2 (C-2″), 172.7(C-1″)] were attached at C-2 and C-3, respectively. This was confirmed by the HMBC correlation of H-3 with C-1″ as

well as H-2 and -3 with C-1. The 3-acetoxypentanoic acid was connected through C-5 to C-1′ of the *p*-substituted phenyl ring, as H-5 showed an HMBC cross-peak with C-2′ and -6′. The absolute configuration at C-3 was established as *S* due to the negative optical rotation by comparison with (*S*)-3-hydroxy-5-phenylpentanoic acid ($[\alpha]_D = -14.5°$).[18] Hence, the structure of 3-*O*-acetylniduloic acid (**7**) is (*S*)-3-acetoxy-5-(*p*-hydroxyphenyl)pentanoic acid.

Ethyl 3-*O*-acetylniduloate (**8**), $[\alpha]_D = -14.4°$, had the molecular formula $C_{15}H_{20}O_5$, hence differing from **7** by a C_2H_4 unit. The structure of compound **8** was readily apparent as an ethyl ester of **7** from its ^1H and ^{13}C NMR spectra. The only difference between the NMR spectra of **8** and **7** was the appearance of an ethyl group in **8** present at δ 1.24 (3H, t, $J = 5.3$ Hz, H-2‴) and 4.13 (2H, q, $J = 5.3$ Hz, H-1‴). Thus, compound **8** is ethyl (*S*)-3-*O*-acetylniduloate.

Methyl 4-*O*-coumaroylquinate (**9**) was isolated as colorless syrup with $[\alpha]_D = -107.4°$. The molecular formula was determined as $C_{17}H_{20}O_8$ by HREIMS at *m/z* 352.1161 $[M]^+$. The IR spectrum showed hydroxyl (3390 cm^{-1}) and carbonyl (1705 cm^{-1}) functional groups. The aromatic region of the ^1H NMR spectrum indicated a *trans*-*p*-coumaroyl (4-hydroxycinnamoyl) moiety at δ 6.36 (1H, d, $J = 15.9$ Hz, H-8′), 6.89 (2H, d, $J = 8.5$ Hz, H-3′ and -5′), 7.54 (2H, d, $J = 8.5$ Hz, H-2′ and -6′), and 7.64 (1H, d, $J = 15.9$ Hz, H-7′). The aliphatic region showed mutually coupled signals at δ 1.96 (1H, dd, $J = 13.6$, 10.4 Hz, H-6_{ax}), 2.09 (2H, m, H-2), 2.17 (1H, dd, $J = 13.6$, 2.8 Hz, H-6_{eq}), 4.33 (2H, m, H-3 and -5), and 4.78 (1H, dd, $J = 9.0$, 2.9 Hz, H-4) for a $-CH_2$-CHCHCHCH$_2-$ fragment. From the chemical shifts of H-3 to H-5, it was clear that C-3 to C-5 were oxygenated. H-2 and -6 showed ^2J HMBC correlations with a deshielded quaternary carbon at δ 76.3 (C-1), bearing a hydroxyl group and establishing a six-membered ring. Furthermore, H-2 and H-6 together with an *O*-methyl group at δ 3.71 showed ^3J correlations with a carboxyl carbon at δ 174.7, indicating that a methoxycarbonyl group was attached to C-1. The above spectroscopic analysis along with a large coupling constant of 9.0 Hz between H-4 and H-5 and a small coupling constant of 2.9 Hz between H-3 and H-4 as well as the negative optical rotation led to the assignment of a methyl quinate moiety. The HMBC connectivity between H-4 and C-9′ confirmed the ester linkage between coumaric acid and the hydroxyl group at C-4. Thus, the structure of **9** was elucidated as methyl 4-*O*-coumaroylquinate. This compound was probably an artifact produced from 4-*O*-coumaroylquinic acid by refluxing the plant material in MeOH.

Vittarilide-A (**10**) was isolated as optically active colorless syrup, $[\alpha]_D = +5.1°$. Its molecular formula of $C_{15}H_{16}O_9$ was determined from HRFABMS data at *m/z* 341.0870 $[M + H]^+$. The ^1H NMR spectrum showed a *trans*-caffeoyl (3,4-dihydroxycinnamoyl) moiety due to an ABX system at δ 6.86 (H, d, $J = 8.3$ Hz, H-5′), 7.03 (1H, dd, $J = 8.3$, 2.0 Hz, H-6′), and 7.15 (1H, d, $J = 2.0$ Hz, H-2′); *trans*-coupled olefinic protons at δ 6.30 (1H, d, $J = 15.9$ Hz, H-8′) and 7.58 (1H, d, $J = 15.9$ Hz, H-7′); and two D_2O exchangeable protons at δ 8.22 and 8.46 (each 1H, br s, 3′- and 4′-OH). The ^1H and ^{13}C signals in the aliphatic region constructed a gluconic acid skeleton due to resonances at δ_H 4.30 (1H, m, H-5), 4.33 (1H, d, $J = 9.3$ Hz, H-2), 4.34 (1H, m, H-6_a), 4.46 (1H, dd, $J = 10.7$, 2.1 Hz, H-6_b), 4.49 (1H, dd, $J = 9.3$, 5.0 Hz, H-3), and 4.63 (1H, dd, $J = 6.3$, 5.0 Hz, H-4) and δ_C 66.4 (C-6), 69.0 (C-5), 74.5 (C-2 and -3), 80.1 (C-4), and 175.3 (C-1). The HMBC correlation of H-6 with C-9′ indicated that the caffeoyl moiety was linked to C-6. The downfield-shifted H-4 and the HMBC connectivities of H-2 to H-4 with C-1 indicated that the gluconic acid cyclized to a γ-lactone. The H-3 *trans* to H-2 and *cis* to H-4 were proven by the larger coupling constant of $J_{2-3} = 9.3$ Hz and the smaller coupling constant of $J_{3-4} = 5.0$ Hz, as well as the presence of a NOE between H-3 and H-4. The positive optical rotation of **10** indicated that it is a derivative of D-glucono-γ-lactone.[19] Therefore, 6-*O*-caffeoyl-D-glucono-γ-lactone was considered to have the structure of vittarilide-A (**10**).

Vittarilide-B (**11**), obtained as an optically active colorless syrup $[\alpha]_D = +4.8°$, had a molecular ion peak at *m/z* 294.0739 from the HREIMS, which matched a formula of $C_{14}H_{14}O_7$. Although the ^1H and ^{13}C NMR spectra of **11** were very similar to those of **10**, differences in the chemical shifts of aliphatic signals were observed. From the ^1H and ^{13}C resonances at δ_H 1.46 (3H, d, $J = 6.3$ Hz, H-5), 4.46 (1H, dq, $J = 7.3$, 6.2 Hz, H-4), 4.66 (1H, d, $J = 7.3$ Hz, H-2), and 5.19 (1H, t, $J = 7.3$ Hz, H-3); δ_C 19.1 (C-5), 73.1 (C-4), 76.7 (C-2), 80.5 (C-3), and 173.4 (C-1), a deoxy five-carbon carbohydrate moiety was indicated. Again, the HMBC correlations of H-2 to H-4 with C-1 indicated the existence of a γ-lactone ring. The NOE between H-3 and H-5 and between H-2 and H-4 supported the *trans* orientation of H-3 with respect to H-2 and -4. These data and the positive optical rotation indicated that the carbohydrate moiety was 5-deoxy-D-arabinono-γ-lactone.[20] The HMBC correlation of H-3 with C-9′ indicated that the caffeoyl group was attached to C-3. Thus, the structure of vittarilide-B (**11**) was 3-*O*-caffeoyl-5-deoxy-D-arabinono-γ-lactone.

Vittariflavone (**12**) was obtained as yellowish crystals with the molecular formula $C_{24}H_{26}O_{12}$ from its HRFABMS at *m/z* 507.1505 $[M + H]^+$. The UV spectrum showed maximum absorptions at 209, 258, and 365 nm, typical for a flavone derivative. In the ^1H NMR spectrum, a very downfield singlet at δ 13.41 was assigned to 5-OH due to intramolecular hydrogen bonding with 4-C=O. A sharp singlet integrated for two protons at δ 7.36 ascribed to H-2′ and -6′ of a symmetrically substituted B-ring. A singlet at δ 7.07 was assigned to H-3, as it showed NOEs with H-2′ and -6′. Two *m*-coupled signals with a 1.5 Hz coupling constant at δ 6.87 and 7.20 were attributed to H-6 and -8, respectively, because the former had an NOE with 5-OH. A characteristic doublet with large coupling constant ($J = 6.8$ Hz) at δ 5.77 assignable to an anomeric proton indicated the presence of a glucopyranose unit in the molecule. The NOE between the anomeric proton H-1″ and H-6, -8 indicated the attachment of glucose to C-7. The three *O*-methyl groups of the B-ring resonated at δ 3.88 (6H, s) and 3.96 (3H, s). Consequently, the structure of **12** was assigned as 5-hydroxy-7-*O*-β-glucopyranosyloxy-3′,4′,5′-trimethoxyflavone.

The isolated compounds **1**, **3**, **5**, **7**, **10**, **12**−**14**, and **16**−**19** were subjected to cytotoxicity evaluation; only 5,7-dihydroxy-3,4,5-trimethoxyflavone (**18**) displayed moderate cytotoxicity against two human cancer cell lines, lung carcinoma (NCI-H460) and central nervous system carcinoma (SF-268), with inhibitions of 89 and 61% at the concentration of 58 μM, respectively. In addition, compounds **1**−**6**, **7**, **10**−**14**, and **17**−**19** were examined for their antioxidant properties using the α,α-diphenyl-β-picrylhydrazyl free radical (DPPH) scavenging assay. Vittarilide-A (**10**), vittarilide-B (**11**), and ethyl 4-*O*-caffeoylquinate (**14**) exhibited moderate scavenging activity, with IC_{50} values of 91, 290, and 234 μM, respectively, compared with the reference, vitamin E (IC_{50}, 350 μM).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. UV spectra were recorded on an Agilent 8453 spectrophotometer. IR spectra were recorded on a Nicolet Magna FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance 300 FT-NMR spectrometer; all chemical shifts were given in ppm from tetramethylsilane as an internal standard. Mass spectra were obtained on a VG 70-250S spectrometer by a direct inlet system.

Plant Material. The whole plant of *Vittaria anguste-elongata* was collected from Nanto Hsien, Taiwan, in November 2002. It was authenticated by Professor C. S. Kuoh, Department of Biology, National Cheng Kung University, Tainan, Taiwan. A voucher specimen (No: PLW-0102) was deposited in the Herbarium of National Cheng Kung University, Tainan, Taiwan.

Extraction and Isolation. The air-dried plants of *V. anguste-elongata* (1.5 kg) were extracted with MeOH (6 × 3 L) under reflux. The combined extracts were concentrated under reduced pressure to give a dark green syrup (250 g). The syrup was then suspended in H_2O and partitioned with hexane, $CHCl_3$, and EtOAc, successively. The $CHCl_3$ extract (25 g) was chromatographed on a silica gel column by eluting with a gradient of hexane−Me_2CO (4:1 to 100% Me_2CO) to give nine fractions. Fraction 4 was chromatographed on silica gel eluting with hexane−EtOAc (3:1) to yield **27** (3 mg). Fraction 5 was chromatographed on silica gel using hexane−EtOAc (3:1) as eluent to obtain **21** (1 mg), **24** (1 mg), **25** (12 mg), and **31** (3 mg). Similarly, fraction 7 gave **20** (6 mg), **23** (33 mg), **26** (1 mg), and **32** (8 mg). The EtOAc extract (8 g) was subjected to column chromatography on Cosmosil 75 C18 and eluted with a gradient from pure H_2O to pure MeOH to give eight fractions. Fraction 1 was chromatographed on silica gel eluting with $CHCl_3$−MeOH−H_2O (5:1:0.1) to give **29** (8 mg). Fractions 2 and 3 were chromatographed on silica gel eluting with $CHCl_3$−MeOH−H_2O (6:1:0.1) to give **13** (116 mg), **10** (22 mg), **28** (8 mg) and **9** (1 mg), **30** (11 mg), **7** (13 mg). Fraction 4 was separated by silica gel chromatography using $CHCl_3$−MeOH−H_2O (5:1:0.6) to give **4** (7 mg), **14** (18 mg), **17** (108 mg), **11** (5 mg), **22** (27 mg), and **3** (98 mg). Fraction 6 was chromatographed on silica gel using the same solvent mixture to yield **1** (8 mg), **2** (2 mg), **5** (18 mg), **6** (4 mg), **15** (1 mg), **8** (1 mg), and **12** (15 mg). Fraction 7 was chromatographed on silica gel eluting with $CHCl_3$−MeOH (6:1) to produce **16** (3 mg). Finally, fraction 8 was chromatographed on silica gel and eluted with $CHCl_3$−MeOH (7:1) to give **18** (2 mg) and **19** (6 mg).

Vittarin-A (1): white crystals; mp 61−63 °C ($CHCl_3$/MeOH); UV (MeOH) λ_{max} (log ϵ) 230 (3.72), 280 (3.37) nm; IR (KBr) ν_{max} 3390, 2930, 1601, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 400M Hz) δ 2.78 (2H, t, J = 7.1 Hz, H-α), 2.83 (2H, m, J = 7.1 Hz, H-β), 3.84 (3H, s, 3′-OCH_3), 3.86 (3H, s, 4′-OCH_3), 4.79 (2H, s, 3- and 5-OH), 6.19 (1H, t, J = 2.0 Hz, H-4), 6.23 (2H, d, J = 2.0 Hz, H-2 and −6), 6.65 (1H, d, J = 1.6 Hz, H-2′), 6.71 (1H, dd, J = 8.1, 1.6 Hz, H-6′), 6.79 (1H, d, J = 8.1 Hz, H-5′); ^{13}C NMR ($CDCl_3$, 100M Hz) δ 37.0 (C-β), 37.9 (C-α), 55.8 (4′-OCH_3), 55.9 (3′-OCH_3), 100.4 (C-4), 108.2 (C-2 and -6), 111.5 (C-5′), 111.8 (C-2′), 120.2 (C-6′), 134.2 (C-1′), 144.9 (C-1), 147.2 (C-4′), 148.7 (C-3′), 156.7 (C-3 and -5); EIMS *m/z* 274 (M^+, 81), 220 (20), 152 (36), 151 (100), 133 (24), 121 (71), 107 (68); HREIMS *m/z* 274.1206 $[M]^+$ (calcd for $C_{16}H_{18}O_4$ 274.1205).

Vittarin-B (2): white crystals; mp 113−115 °C ($CHCl_3$/MeOH); UV ($CHCl_3$) λ_{max} (log ϵ) 242 (3.38), 278 (3.27) nm; IR (KBr) ν_{max} 3355, 2917, 2849, 1594, 1510, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300M Hz) δ 2.77 (2H, m, H-α), 2.82 (2H, m, H-β), 3.79 (3H, s, 4′-OCH_3), 4.73 (2H, s, 3- and 5-OH), 6.19 (1H, t, J = 1.8 Hz, H-4), 6.23 (2H, d, J = 1.8 Hz, H-2 and -6), 6.82 (2H, d, J = 8.4 Hz, H-3′ and -5′), 7.08 (2H, d, J = 8.4 Hz, H-2′ and -6′); ^{13}C NMR ($CDCl_3$, 75M Hz) δ 36.5 (C-β), 38.0 (C-α), 55.3 (4′-OCH_3), 100.4 (C-4), 108.1 (C-2 and -6), 113.7 (C-3′ and-5′), 129.3 (C-2′ and -6′), 133.5 (C-1′), 144.8 (C-1), 156.6 (C-3 and -5), 157.8 (C-4′); EIMS *m/z* 244 (M + H^+, 20), 151 (40), 121 (100), 77 (5); HREIMS *m/z* 244.1102 $[M]^+$ (calcd for $C_{15}H_{16}O_3$ 244.1099).

Vittarin-C (3): yellowish syrup; $[\alpha]_D$ −41.8° (*c* 0.255, MeOH); UV (MeOH) λ_{max} (log ϵ) 214 (4.26), 252 (3.61), 286 (3.41) nm; IR (film) ν_{max} 3375, 2936, 1589, 1512 cm^{-1}; ^1H NMR (pyridine-d_5, 300M Hz) δ 3.05 (2H, t, J = 8.0 Hz, H-β), 3.65 (3H, s, 4′-OCH_3), 3.69 (2H, t, J = 8.0 Hz, H-α), 4.04 (1H, m, H-5″), 4.29−4.49 (5H, m, H-2″, H-3″, H-4″, H-6″), 5.66 (1H, d, J = 7.1 Hz, H-1″), 6.75 (1H, d, J = 2.1 Hz, H-6), 6.89 (2H, d, J = 8.2 Hz, H-3′ and -5′), 7.06 (1H, d, J = 2.1 Hz, H-4), 7.35 (2H, d, J = 8.2 Hz, H-2′ and -6′); ^{13}C NMR (pyridine-d_5, 75M Hz) δ 38.1 (C-β), 39.3 (C-α), 55.2 (4′-OCH_3), 62.3 (C-6″), 71.2 (C-4″), 75.0 (C-2″), 78.5 (C-5″), 78.8 (C-3″), 101.7 (C-1″), 102.7 (C-4), 110.5 (C-6), 111.8 (C-2), 114.2 (C-3′ and -5′), 130.1 (C-2′ and -6′), 136.0 (C-1′), 148.5 (C-1), 158.3 (C-4′), 161.1 (C-5), 166.4 (C-3), 177.7 (2-C=O); FABMS *m/z* 473 ($[M + H]^+$, 19); HR-FABMS *m/z* 473.1425 $[M + H]^+$ (calcd for $C_{22}H_{26}O_{10}Na$, 473.1424).

Vittarin-D (4): yellowish syrup; $[\alpha]_D$ −26.3° (*c* 0.355, MeOH); UV (MeOH) λ_{max} (log ϵ) 216 (3.83), 286 (3.26) nm; IR (film) ν_{max} 3370, 2932, 1588, 1514 cm^{-1}; ^1H NMR (pyridine-d_5, 300M Hz) δ 3.20 (2H, t, J = 8.0 Hz, H-β), 3.71 (3H, s, 4′-OCH_3), 3.75 (3H, s, 3′-OCH_3), 3.90 (2H, t, J = 8.0 Hz, H-α), 4.03 (1H, m, H-5″), 4.36 (4H, m, H-2″, H-3″, H-4″, H-6a), 4.47 (1H, d, J = 12.1 Hz, H-6b), 5.69 (1H, d, J = 7.0 Hz, H-1″), 6.81 (1H, d, J = 2.2 Hz, H-6), 6.83 (1H, d, J = 8.1 Hz, H-5′), 7.05 (1H, d, J = 8.1 Hz, H-6′), 7.15 (1H, d, J = 2.2 Hz, H-4), 7.24 (1H, s, H-2′); ^{13}C NMR (pyridine-d_5, 75M Hz) δ 38.9 (C-β), 39.6 (C-α), 56.0(3′-OCH_3), 56.2 (4′-OCH_3), 62.2 (C-6″),71.2 (C-4″), 75.1 (C-2″), 78.5 (C-3″), 78.7 (C-5″), 101.7 (C-1″), 102.7 (C-4), 109.7 (C-6), 112.8 (C-5′), 113.5 (C-2′), 113.7 (C-2), 121.2 (C-6′),137.2 (C-1′), 148.1 (C-4′), 148.4 (C-1), 149.9 (C-3′), 160.5 (C-5), 167.3 (C-3), 175.9 (2-C=O); FABMS *m/z* 503 ($[M + H]^+$, 1), 413 (36), 391 (18); HRFABMS *m/z* 503.1527 $[M + H]^+$ (calcd for $C_{23}H_{28}O_{11}Na$, 503.1529).

Vittarin-E (5): white crystals; mp 139−140 °C (MeOH); UV (MeOH) λ_{max} (log ϵ) 217 (4.51), 260 (3.96), 287 (3.78), 301 (3.71), 353 (3.24) nm; IR (KBr) ν_{max} 3374, 2938, 1604, 1513 cm^{-1}; ^1H NMR (CD_3OD, 300M Hz) δ 2.79 (4H, t, J = 7.4 Hz, 2 × H-β), 3.18 (4H, t, J = 7.4 Hz, 2 × H-α), 3.79 (12H, s, 2 × 3′- and 4′-OCH_3), 6.11 (2H, d, J = 2.5 Hz, 2 × H-6), 6.15 (2H, d, J = 2.5 Hz, 2 × H-4), 6.74 (2H, dd, J = 8.0, 2.1 Hz, 2 × H-6′), 6.76 (2H, d, J = 2.1 Hz, 2 × H-2′), 6.82 (2H, d, J = 8.0 Hz, 2 × H-5′); ^{13}C NMR (CD_3OD, 75M Hz) δ 39.0 (2 × C-β), 40.0 (2 × C-α), 56.4 and 56.6 (2 × 4′- and 3′-OCH_3), 101.9 (2 × C-4), 106.6 (2 × C-2), 111.8 (2 × C-6), 113.2 (2 × C-5′), 113.8 (2 × C-2′), 121.8 (2 × C-6′), 136.9 (2 × C-1′), 148.6 (2 × C-4′), 149.0 (2 × C-1), 150.2 (2 × C-3′), 162.9 (2 × C-5), 166.6 (2 × C-3); FABMS *m/z* 569 (M + Na^+, 1), 275 (18); HRFABMS *m/z* 569.2149 $[M + Na]^+$ (calcd for $C_{32}H_{34}O_8Na$, 569.2151).

Vittarin-F (6): white amorphous powder; $[\alpha]_D$ −5.4° (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ϵ) 282 (3.60) nm; IR (KBr) ν_{max} 3386, 2926, 1701, 1617, 1592, 1515 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 2.56 (2H, t, J = 7.8 Hz, H-β), 2.73 (2H, t, J = 7.8 Hz, H-α), 2.76 (1H, dd, J = 15.5 and 2.2 Hz, H-3a), 2.98 (1H, dd, J = 15.5, 6.5 Hz, H-3b), 3.73 (3H, s, 3″-OCH_3), 3.74 (3H, s, 4″-OCH_3), 4.34 (1H,dd, J = 6.5, 2.2 Hz, H-4), 6.46 (1H, s, H-8), 6.47 (1H, dd, J = 8.1, 1.9 Hz, H-6′), 6.54 (1H, d, J = 1.9 Hz, H-2′), 6.59 (1H, s, H-5), 6.60 (1H, dd, J = 7.9, 2.1 Hz, H-6″), 6.62 (1H, d, J = 2.1 Hz, H-2″), 6.74 (1H, d, J = 8.1 Hz, H-5′), 6.79 (1H, d, J = 7.9 Hz, H-5″), 7.86 (2H, br s, 2×-OH), 8.60 (1H, brs, −OH); ^{13}C NMR (acetone-d_6, 75 MHz) δ 35.6 (C-α), 37.4 (C-β and C-4), 39.0 (C-3), 56.1 (3″- and 4″-OCH_3), 102.5 (C-8), 113.0 (C-2″), 113.4 (C-5″), 113.6 (C-5), 114.9 (C-2′), 115.8 (C-10), 116.4 (C-5′), 119.2 (C-6′), 121.1 (C-6″), 134.7 (C-1′), 135.1 (C-1″), 142.6 (C-6), 145.1 (C-4′), 146.2 (C-3′), 148.7 (C-4″), 150.2 (C-3″), 154.1 (C-9), 158.3 (C-7), 167.7 (C-2); EIMS *m/z* 436 (M^+, 5), 420 (9), 394 (52), 243 (33), 194 (16), 151 (100), 110 (20); HREIMS *m/z* 436.1525 $[M]^+$ (calcd for $C_{25}H_{24}O_7$, 436.1522).

3-*O*-Acetylniduloic acid (7): colorless syrup; $[\alpha]_D$ −47.6° (*c* 0.31, MeOH); UV (MeOH) λ_{max} (log ϵ) 222 (3.66), 250 (3.19), 286 (3.23), 333 (3.33) nm; IR (film) ν_{max} 3251, 2932, 1716, 1575, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.89 (2H, m, H-4), 1.99 (3H, s, H-2″), 2.40 (1H, dd, J = 14.2, 6.5 Hz, H-2a), 2.51 (1H, dd, J = 14.2, 6.5 Hz, H-2b), 2.56 (2H, m, H-5), 5.26 (1H, quintet, J = 6.5 Hz, H-3), 6.67 (2H, d, J = 8.3 Hz, H-3′ and

-5′), 6.99 (2H, d, J = 8.3 Hz, H-2′ and -6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2 (C-2″), 31.8 (C-5), 37.5 (C-4), 43.7 (C-2), 73.9 (C-3), 116.1 (C-3′ and -5′), 130.2 (C-2′ and -6′), 133.9 (C-1′), 156.4 (C-4′), 172.7 (C-1″), 178.6 (C-1); EIMS *m/z* 252 (M^+, 5), 192 (57), 147 (7), 133 (100), 121(8), 107 (70), 91 (9), 77(18); HREIMS *m/z* 252.0995 $[M]^+$ (calcd for $C_{13}H_{16}O_5$, 252.0998).

Ethyl 3-*O*-acetylniduloate (8): colorless syrup; $[\alpha]_D$ −14.4° (*c* 0.04, MeOH); UV (MeOH) λ_{max} (log ϵ) 278 (3.63), 312 (3.30) nm; IR (film) ν_{max} 3369, 2930, 1737, 1613, 1516 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300M Hz) δ 1.24 (3H, t, J = 5.3 Hz, H-2‴), 1.92 (2H, m, H-4), 2.03 (3H, s, H-2″), 2.58 (4H, m, H-2 and -5), 4.13 (2H, q, J = 5.3 Hz, H-1‴), 5.24 (1H, quintet, J = 6.4 Hz, H-3), 6.75 (2H, d, J = 8.4 Hz, H-3′and -5′), 7.03 (2H, d, J = 8.4 Hz, H-2′ and -6′); ^{13}C NMR ($CDCl_3$, 75M Hz) δ 14.2 (C-2‴), 21.1 (C-2″), 30.6 (C-5), 35.9 (C-4), 39.3 (C-2), 60.7 (C-1‴), 70.1 (C-3), 115.3 (C-3′ and -5′), 129.4 (C-2′ and -6′), 133.3 (C-1′), 153.8 (C-4′), 170.3 (C-1), 170.4 (C-1″); EIMS *m/z* 280 (M^+, 4), 235 (9), 220 (100), 191 (9), 175 (67), 146 (100), 133 (100), 120 (22), 107 (100), 91 (14), 77 (26); HREIMS *m/z* 280.1311 $[M]^+$ (calcd for $C_{15}H_{20}O_5$, 280.1311).

Methyl 4-*O*-comaroylquinate (9): colorless syrup; $[\alpha]_D$ −107.4° (*c* 0.035, MeOH); UV (MeOH) λ_{max} (log ϵ) 210 (3.96), 314 (4.12) nm; IR (film) ν_{max} 3390, 2956, 2925, 1705, 1632, 1604 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.96 (1H, dd, J = 13.6, 10.4 Hz, H-6$_{ax}$), 2.09 (2H, m, H-2), 2.17 (1H, dd, J = 13.6, 2.8 Hz, H-6$_{eq}$), 3.71 (3H, s, −OCH_3), 4.21 (1H, d, J = 4.7 Hz, 5-OH), 4.33 (2H, m, H-3 and −5), 4.49 (1H, d, J = 6.6 Hz, 3-OH), 4.78 (1H,dd, J = 9.0, 2.9 Hz, H-4), 5.02 (1H, s, 1-OH), 6.36 (1H, d, J = 15.9 Hz, H-8′), 6.89 (2H, d, J = 8.5 Hz, H-3′ and -5′), 7.54 (2H, d, J = 8.5 Hz, H-2′ and -6′), 7.64 (1H, d, J = 15.9 Hz, H-7′); ^{13}C NMR (acetone-d_6, 75 M Hz) δ 38.4 (C-2), 42.6 (C-6), 52.5 (−OCH_3), 65.0 (C-5), 69.0 (C-3), 76.3 (C-1), 79.0 (C-4), 116.0 (C-8′), 116.7 (C-3′ and −5′), 127.3 (C-1′), 130.9 (C-2′ and -6′), 145.3 (C-7′), 160.9 (C-4′), 167.3 (C-9′), 174.7 (C-7); EIMS *m/z* 352 (M^+, 10), 320 (5), 258 (5), 164 (35), 147 (100), 119 (19), 107 (8), 91 (21); HREIMS *m/z* 352.1161 $[M]^+$ (calcd for $C_{17}H_{20}O_8$, 352.1158).

Vittarilide-A (10): colorless syrup; $[\alpha]_D$ +5.1° (*c* 1.075, MeOH); UV (MeOH) λ_{max} (log ϵ) 221 (3.40), 245 (3.24), 269 (3.26), 329 (3.33) nm; IR (film) ν_{max} 3382, 2959, 1704, 1633, 1604, 1518 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 4.30 (1H, m, H-5), 4.33 (1H, d, J = 9.3 Hz, H-2), 4.34 (1H, m, H-6$_a$), 4.46 (1H, dd, J = 10.7, 2.1 Hz, H-6$_b$), 4.49 (1H, dd, J = 9.3, 5.0 Hz, H-3), 4.63 (1H, dd, J = 6.3, 5.0 Hz, H-4), 6.30 (1H, d, J = 15.9 Hz, H-8′), 6.86 (H, d, J = 8.3 Hz, H-5′), 7.03 (1H, dd, J = 8.3, 2.0 Hz, H-6′), 7.15 (1H, d, J = 2.0 Hz, H-2′), 7.58 (1H, d, J = 15.9 Hz, H-7′), 8.22 and 8.46 (each 1H, br s, 3′- and 4′-OH); ^{13}C NMR (acetone-d_6, 75 MHz) δ 66.4 (C-6), 69.0 (C-5), 74.5 (C-2 and -3), 80.1 (C-4), 115.1 (C-2′) 115.3 (C-8′), 116.3 (C-5′), 122.5 (C-6′), 127.5 (C-1′), 146.0 (C-7′), 146.2 (C-3′), 148.7 (C-4′), 167.5 (C-9′), 175.3 (C-1); FABMS *m/z* 341 ($[M + H]^+$, 6), 307 (12), 289 (10), 279 (20); HRFABMS *m/z* 341.0870 $[M + H]^+$ (calcd for $C_{15}H_{17}O_9$, 341.0873).

Vittarilide-B (11): colorless syrup; $[\alpha]_D$ +4.8° (*c* 0.051, MeOH); UV (MeOH) λ_{max} (log ϵ) 218 (3.71), 251 (3.63), 297 (3.54), 330 (3.64) nm; IR (film) ν_{max} 3289, 2360, 2342, 1703, 1603, 1259 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.46 (3H, d, J = 6.3 Hz, H-5), 4.46 (1H, dq, J = 7.3, 6.2 Hz, H-4), 4.66 (1H, d, J = 7.3 Hz, H-2), 5.19 (1H, t, J = 7.3 Hz, H-3), 6.32 (1H, d, J = 15.8 Hz, H-8′), 6.87 (1H, d, J = 8.3 Hz, H-5′), 7.07 (1H, dd, J = 8.3, 1.9 Hz, H-6′), 7.18 (1H, d, J = 1.7 Hz, H-2′), 7.63 (1H, d, J = 15.8 Hz, H-7′), 8.45 (2H, br s, 3′- and 4′-OH); ^{13}C NMR (acetone-d_6, 75 MHz) δ 19.1 (C-5), 73.1 (C-4), 76.7 (C-2), 80.5 (C-3), 114.2 (C-8′), 115.3 (C-2′), 116.4 (C-5′), 122.9 (C-6′), 127.3 (C-1′), 146.4 (C-3′), 147.4 (C-7′), 149.2 (C-4′), 166.9 (C-9′), 173.4 (C-1); EIMS *m/z* 294 (M^+, 18), 180 (21), 163 (64), 151 (37), 147 (28), 136 (100), 107 (19), 89 (39); HREIMS *m/z* 294.0739 $[M]^+$ (calcd for $C_{14}H_{14}O_7$, 294.0740).

Vittariflavone (12): yellowish crystals; mp 234−236 °C (MeOH); $[\alpha]_D$ −42.4° (*c* 0.033, pyridine); UV (MeOH) λ_{max} (log ϵ) 209 (3.40), 258 (2.86), 365 (2.54) nm; IR (KBr) ν_{max} 3383, 1661, 1616 cm^{-1}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 3.88 (6H, s, 3′ and 5′-OCH_3), 3.96 (3H, s, 4′-OCH_3), 4.15 (1H, m, H-5″), 4.34 (4H, m, H-2″, 3″, 4″, 6a″), 4.57 (1H, d, J = 11.6 Hz, H-6b″), 5.77 (1H, d, J = 6.8 Hz, H-1″), 6.87 (1H, d, J = 1.5 Hz, H-6), 7.07 (1H, s, H-3), 7.20 (1H, d, J = 1.5 Hz, H-8), 7.36 (2H, s, H-2′ and -6′), 13.41 (1H, s, 5-OH); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 56.5 (3′- and 5′-OCH_3), 60.9 (4′-OCH_3), 62.4 (C-6″), 71.3 (C-4″), 74.9 (C-2″), 78.5 (C-3″), 79.3 (C-5″), 95.8 (C-8), 101.0 (C-6), 101.9 (C-1″), 104.9 (C-2′ and -6′), 106.1 (C-3), 106.8 (C-10), 126.9 (C-1′), 142.4 (C-4′), 154.3 (C-3′ and -5′), 158.0 (C-9), 162.2 (C-5), 164.4 (C-2 and -7), 183.0 (C-4); FABMS *m/z* 507 ($[M + H]^+$, 9), 345 (31), 279 (29), 207 (34); HRFABMS *m/z* 507.1505 $[M + H]^+$ (calcd for $C_{24}H_{27}O_{12}$, 507.1503).

Cytotoxicity Assay. The cytotoxicity assay was carried out according to the procedure described in the literature.[21]

Antioxidant Assay. The antioxidant assays were based on methods reported by Ko et al.[22] and Mellors et al.[23] The percentage values of inhibition were recorded after incubating for 30 min.

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