CHEMICAL CONSTITUENTS FROM METHANOLIC EXTRACT OF GARCINIA MACKEANIANA LEAVES AND THEIR ANTIOXIDANT ACTIVITY

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Abstract. The phytochemical investigation of the methanolic extract of Garcinia mackeaniana Craib. leaves led to the isolation and determination of five known compounds, including one benzophenone 4,3',4'-trihydroxy-2,6-dimethoxybenzophenone (1), two flavone C-glucosides, vitexin (2) and 2''-O-acetylvitexin (3), one biflavone, amentoflavone (4), and one phenolic compound, methyl protocatechuate (5). The chemical structures of compounds 1-5 were characterized by the NMR-spectral methods. All isolated compounds were separated from G. mackeaniana for the first time. Benzophenone derivative 1 has shown the IC50 value of 14.97 ± 0.8 µg/mL in the DPPH-antioxidant examination.

Keywords: Garcinia mackeaniana, leaves, phytochemistry, antioxidant activity.

Classification numbers: 1.1.1, 1.2.1.

1. INTRODUCTION

Genus Garcinia is a large genus of the flowering plants which belong to the family Clusiaceae. Plants of this genus with about 450 species are now native to Asia, Australia, America, and Southern Africa [1]. Garcinia species have always contributed valuable properties as traditional medicines to the food chemistry and pharmacology. For instance, the decoction of G. cambogia fruit rind was employed for rheumatism treatment, and bowel complaints [2]. The fruit of mangosteen (G. mangostana) is now well-known in food chemistry because of its distinctive and pleasant taste [3]. Polyisoprenylated benzophenone derived from some Garcinia species, namely garcinol, was recommended for the antioxidant therapeutic targets [4]. Phytochemical investigations of Garcinia plants indicated that xanthones, flavonoids, and benzophenones were major components [1]. Among about 30 Garcinia species distributed in
Viet Nam, *G. mackeaniana* was selected for phytochemical investigation and antioxidant examination [5]. As part of phytochemical investigation [6], we now describe the isolation, structural elucidation of five known compounds from *G. mackeaniana* and their DPPH-radical quenching activity.

2. MATERIALS AND METHODS

2.1. General experimental procedures

ESI-MS spectra were recorded on Thermo Scientific LTQ Orbitrap XL spectrometer (USA). NMR spectra were obtained from Bruker 500 MHz spectrometer (125 MHz for $^1$C and at 500 MHz for $^1$H). Silica gel (40 - 63 µm), Sephadex LH-20 (25 - 100 µm), and RP-18 (150 µm, Kyoto-Japan) were applied for column chromatography (CC), while silica gel 60 F$_{254}$ (Merck) was used for TLC analysis. Compounds were detected by UV lamp (254 and 365 nm), and by spraying plates with indicators (10 % H$_2$SO$_4$ and vanillin).

2.2. Plant materials

The leaves of *Garcinia mackeaniana* Craib, were collected in Son La, Viet Nam in January 2018, and were identified by Dr. Nguyen Quoc Binh, Institute of Ecology and Biological Resources. A voucher specimen (VN-1641) was deposited in Department of Applied Biochemistry, Institute of Chemistry.

2.3. Extraction and isolation

The dried leaves powder of *G. mackeaniana* (1.3 kg) was immersed with MeOH (10 L × 3 times) for 1 h at 50 °C. The MeOH solution was then concentrated under decreased pressure to give a crude MeOH residue (89.1 g). This part was chromatographed on a silica gel column (10 × 50 cm, 182.0 g), eluting with a stepwise gradient of *n*-hexane-CH$_2$Cl$_2$ (1:1→0:1, v/v) and CH$_2$Cl$_2$-MeOH (9:1→0:1, v/v), to afford 15 fractions (MF.1-MF.15). Fraction MF.9 (0.9 g) was subjected to silica gel CC [CH$_2$Cl$_2$-EtOAc (3:1, v/v)], to afford 4 fractions (MF.91-MF.94). Fraction Fr.91 (40 mg) was continued to separate by a RP-18 column [MEOH-H$_2$O (1:1, v/v)], to give compound 1 (8.0 mg). Compound 4 (7.0 mg) was separated from fraction MF.92 (0.3 g) by washing with MeOH. Fraction MF.11 (0.5 g) was further chromatographed on a silica gel column [CH$_2$Cl$_2$-CH$_2$COCH$_3$ (1:1, v/v)], to give compounds 5 (2.5 mg) and 3 (15.0 mg). Finally, fraction MF.12 (0.7 g) was re-chromatographed on a silica gel column [CH$_2$Cl$_2$-MeOH (30:1, v/v)], to obtain compound 2 (15.0 mg).

4,3′,4′-Trihydroxy-2,6-dimethoxybenzophenone (1): Yellow amorphous powders; ESI-MS: $m/z$ 291 [M+H]$^+$ (calc for C$_{15}$H$_{15}$O$_{6}$, 291); $^1$H-NMR (500 MHz, CD$_3$OD, $\delta_{H}$ ppm): 6.17 (2H, s, H-3, H-5), 7.27 (1H, d, 2.5 Hz, H-2′), 7.17 (1H, dd, 2.5, 8.0 Hz, H-6′), 6.77 (1H, d, 8.0 Hz, H-5′), and 3.67 (6H, s, 2-OCH$_3$, 6-OCH$_3$); $^{13}$C-NMR (125 MHz, CD$_3$OD, $\delta_{C}$ ppm): 197.0 (CO), 161.8 (C-4), 160.1 (C-2, C-6), 152.4 (C-5′), 132.2 (C-3′), 124.7 (C-6′), 117.3 (C-2′), 115.7 (C-5′), 111.1 (C-1′), 92.9 (C-3, C-5), and 56.11 (2-OCH$_3$, 6-OCH$_3$).

Vitexin (2): Yellow amorphous powders; ESI-MS: $m/z$ 433 [M+H]$^+$ (calc for C$_{21}$H$_{23}$O$_{10}$, 433); $^1$H-NMR (DMSO-$d_6$, 500 MHz, $\delta_{H}$ ppm): 13.14 (1H, s, 5-OH), 8.00 (2H, brd, 8.5 Hz, H-2′, H-6′), 6.90 (2H, d, 8.5 Hz, H-3′, H-5′), 6.74 (1H, s, H-3), 6.23 (1H, s, H-6), 4.72 (1H, d, 9.5 Hz, H-1′), 3.85 (1H, t, 9.0 Hz, H-2′), 3.71 (1H, br, 11.0 Hz, H-6′), 3.52 (1H, dd, 6.0, 12.0 Hz, H$_{2′}$-6′), and 3.25-3.36 (2H, m, H-4′, H-5′); $^{13}$C-NMR (DMSO-$d_6$, 125 MHz, $\delta_{C}$ ppm): 181.9 (C-4), 124.7 (C-3′), 117.3 (C-2′), 115.7 (C-5′), 111.1 (C-1), 92.9 (C-3, C-5), and 56.11 (2-OCH$_3$, 6-OCH$_3$).
163.8 (C-2), 162.8 (C-7), 161.2 (C-4), 160.4 (C-5), 156.0 (C-8a), 129.0 (C-2', C-6'), 121.6 (C-1'), 115.8 (C-3', C-5'), 104.6 (C-4a, C-8), 102.4 (C-3), 98.4 (C-6), 81.8 (C-5'), 73.5 (C-1'), 70.9 (C-2'), 78.7 (C-3'), 70.6 (C-4'), and 61.3 (C-6').

2''-O-Acetylvitexin (3): Yellow amorphous powders; ESI-MS: *m/z* 475 [M+H]+ (calcd for C_{32}H_{32}O_{11}, 475); 1H-NMR (500 MHz, CD_{3}OD, δ_{H} ppm): 8.05 (2H, d, 8.5 Hz, H-2', H-6'), 6.98 (1H, d, 8.5 Hz, H-3', H-5'), 6.62 (1H, s, H-3), 6.24 (1H, s, H-6), 5.56 (1H, m, H-2''), 5.10 (1H, d, 10.0 Hz, H-1''), 4.02 (1H, dd, 2.0, 12.0 Hz, H-6''), 3.83 (1H, dd, 5.5, 12.0 Hz, H-6''), 3.72 (1H, m, H-3''), 3.52 (1H, m, H-5''), and 1.80 (3H, s, CH_{3}CO); 13C-NMR (CD_{3}OD, 125 MHz, δ_{C} ppm): 184.1 (C-4), 172.0 (CH_{3}CO), 166.7 (C-2), 164.1 (C-7), 163.0 (C-5), 162.7 (C-4'), 158.6 (C-8a), 130.1 (C-2', C-6'), 123.7 (C-1'), 117.0 (C-3', C-5'), 105.7 (C-4a), 103.7 (C-3', C-8), 99.1 (C-6), 83.1 (C-5''), 77.8 (C-3''), 74.1 (C-2''), 73.0 (C-1''), 72.3 (C-4''), 63.0 (C-6''), and 20.5 (CH_{3}CO).

Amentoflavone (4): Yellow amorphous powders; ESI-MS: *m/z* 539 [M+H]+ (calcd for C_{30}H_{29}O_{10}, 539); 1H-NMR (DMSO-d_{6}, 500 MHz, δ_{H} ppm): 13.10 (1H, s, 5''-OH), 12.98 (1H, s, 5-OH), 8.02 (1H, d, 2.5 Hz, H-2), 7.99 (1H, d, 2.5, 9.0 Hz, H-6'), 7.58 (2H, d, 8.5 Hz, H-2'', H-6''), 7.12 (1H, d, 9.0 Hz, H-5'), 6.82 (1H, s, H-3), 6.77 (1H, s, H-3''), 6.70 (2H, d, 8.5 Hz, H-3'', H-5''), 6.44 (1H, d, 2.0 Hz, H-8), 6.37 (1H, s, H-6''), and 6.18 (1H, d, 2.0 Hz, H-6); 13C-NMR (DMSO-d_{6}, 125 MHz, δ_{C} ppm): 182.1 (C-4'), 181.8 (C-4), 164.2 (C-7), 164.0 (C-2), 163.7 (C-2''), 162.9 (C-7), 161.5 (C-5), 161.0 (C-4''), 160.6 (C-5''), 160.1 (C-4'), 157.4 (C-8a), 154.6 (C-8''), 154.5 (C-2'), 131.5 (C-2'), 128.2 (C-2'', C-6''), 127.7 (C-6'), 121.5 (C-1''), 120.7 (C-1'), 120.4 (C-3'), 116.5 (C-5'), 115.8 (C-3'', C-5''), 104.3 (C-8''), 103.8 (C-4a), 103.5 (C-4'a), 102.9 (C-3), 102.6 (C-3''), 99.0 (C-5''), 98.9 (C-6), and 94.1 (C-8).

Methyl protocatechuate (5): Yellow amorphous powder; ESI-MS: *m/z* 169 [M+H]+ (calcd for C_{5}H_{6}O_{2}, 169); 1H-NMR (CD_{3}OD, 500 MHz, δ_{H} ppm): 7.43 (1H, dd, 2.0, 8.0 Hz, H-6), 7.42 (1H, d, 2.0 Hz, H-2), 6.82 (1H, d, 8.0 Hz, H-5), and 3.85 (3H, s, OCH_{3}); 13C-NMR (CD_{3}OD, 125 MHz, δ_{C} ppm): 167.5 (CO), 150.0 (C-4), 144.8 (C-3), 122.2 (C-1), 121.2 (C-6'), 116.0 (C-5), 114.5 (C-2), and 50.8 (OCH_{3}).

2.4. DPPH-antioxidant assay

Free radical quenching assay of the isolated compounds 1-5 has been carried out by 1,1-diphenyl-2-picryl hydrazyl (DPPH) [7-9]. Briefly, DPPH (0.1 mM) was diluted in methanol. 200 µL of this solution was added to 1.3 µL of various concentrations of 1-5 in DMSO (128.0, 32.0, 8.0, and 2.0 µg/mL). The mixture was performed by a 96-well plate at 25 °C in 30 min. Then, absorbance was determined by Biotek tool (at 517 nm). The percentage of DPPH quenching activity was computed by the following formula:

\[
\text{Inhibitory percentage SC} = \frac{[\text{A}_0 - \text{A}_1]}{\text{A}_0} \times 100.
\]

where \(A_0\) was defined as the absorbance of control reaction, and \(A_1\) represented for the absorbance in the presence of test or standard sample.

Each experiment was repeated three times, while resveratrol was used as a reference compound. The EC_{50} value, also known as the concentration of tested samples that induced half maximal response has been calculated from linear regression of the serial SC values versus the concentrations by using Table Curve 2Dv4.

3. RESULTS AND DISCUSSION

3.1. The NMR-structural elucidation
Compound 1 was separated as yellow amorphous powders. The $^1$H, and $^{13}$C-NMR spectral data of 1 revealed a pattern of a benzophenone derivative. In detail, the $^1$H-NMR spectrum was composed of two superimposed singlet proton signals H-3 and H-5 ($\delta_H$ 6.17), one ABX spin system of $\delta_H$ 6.77, d, 8.0 Hz, 7.17, dd, 2.5, 8.0 Hz, and 7.27, d, 2.5 Hz, and two superimposed singlet methoxy groups at $\delta_H$ 3.67. It suggested that the chemical structure 1 included a symmetrically 1,2,4,6-tetrasubstituted phenyl unit, and another 1,3,4-trisubstituted phenyl unit. The $^{13}$C-NMR data contained two methoxy groups at $\delta_C$ 56.11, five aromatic methines at $\delta_C$ 92.9-124.7 ppm, six aromatic carbons at $\delta_C$ 146.2-160.1 ppm, and a carbonyl group at $\delta_C$ 197.0. The structure of 1 was supported by 2D-NMR evidence, in which the key HBMC correlations H-3 ($\delta_H$ 6.17)/C-1 ($\delta_C$ 111.1), C-2 ($\delta_C$ 160.1), and C-4 ($\delta_C$ 161.8), H-5 ($\delta_H$ 6.17)/C-1, C-4, and C-6 ($\delta_C$ 160.1), 2-OCH$_3$/C-2, 6-OCH$_3$/C-6 confirmed the appearance of 2,6-dimethoxy-4-hydroxyphenyl unit. Similarly, the remaining 1,3,4-substituted phenyl moiety was highlighted with the key HMBC cross-peaks H-5'/C-1', and C-3', H-2' and H-6'/C-4'. The key HMBC correlations H-2' and H-6'/CO implied that two phenyl units were connected through the carbonyl group. From these findings and comparing with literature [10], compound 1 was determined to be 4,3',4'-trihydroxy-2,6-dimethoxybenzophenone.

Figure 1. Isolated compounds from G. mackeaniana leaves and their key HMBC correlations.

Compound 2 was isolated as yellow amorphous powders. The positive ESI-MS spectrum showed the proton adduct ion at $m/z$ 433 [M+H]$^+$, which alongside the $^{13}$C-NMR data were consistent with the molecular formula of C$_{21}$H$_{20}$O$_{10}$. The $^1$H-NMR spectral data of 2 were characteristic of a flavone C-glycoside, in which two singlet signals resonating at $\delta_H$ 6.74 and $\delta_H$ 6.23 were assigned to aromatic methine protons H-3 and H-6, respectively. A symmetric phenyl unit (B ring of flavone) was found to appear at $\delta_H$ 8.00 (2H, brd, 8.5 Hz, H-2', H-6'), and $\delta_H$ 6.90.
(2H, d, 8.5 Hz, H-3', H-5'). The sugar unit of 2 with chemical shifts at δ_H 3.25-4.72 ppm, and coupling constant J = 9.0 Hz of the anomic proton have demonstrated a β-D-glucopyranosyl unit [11-13]. The 2D-NMR spectroscopies were in agreement with the findings in the 1D-NMR (Figure 1). The chromene ring was formulated with HMBC correlations H-3 (δ_H 6.74)/C-2 (δC 163.8), C-4 (δC 181.9), and C-4a (δC 104.6), H-6 (δ_H 6.23)/C-4a, C-5 (δC 160.4), and C-8 (δC 104.6), whereas ring B was established and linked to carbon C-2 due to the key HMBC correlations between H-2' and H-6' (δ_H 8.00), H-3' and H-5' (δ_H 6.90)/C-4, and H-2' and H-6'/C-2. The important HMBC cross peaks H-1''/C-8, and C-8a confirmed that anomic C-1" directly connected to C-8. Based on these findings and comparing with literature, compound 2 was elucidated as vitexin [14].

Compound 3 was isolated as yellow amorphous powders. The 1H and 13C-NMR spectral data of 3 were very similar to those of 2, except for the presence of acetyl group at δ_H 1.80 (3H, s, CH3CO) in the 1H-NMR, and at δ_C 172.0 (CH3CO) and δ_C 20.5 (CH3CO) in the 13C-NMR. The connectivity between the acetoxy group and carbon C-2'' was determined by the HMBC correlation H-2''/CO (Figure 1). The chemical structure of 3 was further confirmed by the positive ESI-MS spectrum. The adduct ion at m/z 475 [M+H]+ in the ESI-MS assigned to the molecular formula of 3 was to be C23H22O11. Based on these findings, and comparing with literature data, compound 3 was identified to be 2"-O-acetylvetexin [15].

Compound 4 was separated as yellow amorphous powders, and had the molecular formula C30H18O10 due to the observation of the proton adduct ion at m/z 539 [M+H]+ in the positive ESI-MS spectrum. The 1H-NMR data of 4 showed the characteristics of a biflavone. In comparison with compounds 2-3, glycosides units of compounds 2-3 were replaced by a flavone unit [three aromatic protons at δ_H 6.82 (H-3), δ_H 6.18 (H-6), and 6.44 (H-8), and a ABX spin system at δ_H 7.12 (1H, d, 9.0 Hz, H-5'), δ_H 7.99 (1H, d, 2.5, 9.0 Hz, H-6'), and δ_H 8.02 (1H, d, 2.5 Hz, H-2')] in 4. The 13C-NMR data of 4 contained 30 carbon signals, which were assigned to twelve aromatic methine carbons, sixteen aromatic carbons, and two carbonyl carbons. The chemical structure of 4 was further confirmed by the 2D-NMR data (HSQC, and HMBC) (Figure 1). Especially, the connectivity between two monomeric flavone units was identified by the key HMBC J^1-correlation from H-2' to C-8", as well as the key HMBC W-shape correlations from H-5' to C-8", and from H-6" to C-3'. In comparison with literature data, isolated compound 4 was determined to be a biflavone, which was trivially named amentoflavone [16]. Secondary metabolite 4 has ever been isolated from various Garcinia species, such as G. brevipedicellata stem heartwoods, or G. livingstonei leaves, however, it was now found in G. mackeaniana [17, 18] for the first time.

Compound 5 was obtained as yellow amorphous powders. The 1H-NMR spectrum of 5 established an ABX spin system of H-5 (δ_H 6.82, d, 8.0 Hz), H-6 (δ_H 7.43, dd, 2.0, 8.0 Hz), and H-2 (δ_H 7.42, d, 2.0 Hz), and one methoxy singlet signal at δ_H 3.85. Therefore, it can be concluded that isolated compound 5 was to be a phenolic compound type of 1,3,4-trisubstituted benzene. Based on the 13C-NMR/DEPT data [three methines at δ_C 114.5 (C-2), δ_C 116.0 (C-5), and δ_C 122.2 (C-6), four carbons at δ_C 121.2 (C-1), δ_C 144.8 (C-3), δ_C 150.0 (C-4), and δ_C 167.5 (CO), together with one methoxy group at δ_C 50.8 (OCH3)], and comparison with literature compound [19], compound 5 was unambiguously determined to be methyl 3,4-dihydroxybenzoate, which was trivially named methyl protocatechuate. Despite its availability in nature, this is the first time this compound was found in genus Garcinia.

3.2. DPPH-antioxidant assay
All isolated compounds 1-5 were subjected to antioxidative examination with the target of DPPH-radical scavenging assessment. Compounds 2-5 failed to capture DPPH radicals at any concentrations (data not shown). In contrast, compound 1 showed the strong EC$_{50}$ value of 14.97±0.8 µg/mL, as compared with that of the positive control (IC$_{50}$ 11.61 ± 0.09 µg/mL). As shown in Figure 2, at the concentration of 128.0 mg/mL, benzophenone 1 completely controlled DPPH with SC = 100%. It is noticeable that benzophenones (compound 1) derived from *Garcinia* plants are better than flavone glycosides and biflavones (compounds 2-4), and phenols (compound 5) in antioxidant treatments.

4. CONCLUSIONS

The present results provide information on the phytochemical investigation and DPPH-antioxidative assay relating to Vietnamese *Garcinia mackeaniana* species. From methanolic extract, five known compounds, comprising of one benzophenone 4,3',4'-trihydroxy-2,6-dimethoxybenzophenone (1), two flavone C-glucosides vitexin (2) and its 2''-O-acetyl derivative (3), one biflavone amentoflavone (4), and one mono-phenol methyl protocatechuate (5) were isolated. This is the first time we report the isolation of these compounds from *G. mackeaniana*. Given strong IC$_{50}$ value in DPPH assay, benzophenone 1 and analogs derived *Garcinia* plants can become promising agents for antioxidant problems.

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