Flavonoids from the leaves and heartwoods of *Artocarpus lowii* King and their bioactivities

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**ABSTRACT**
A new dihydrochalcone, 2′,4′-dihydroxy-3,4-(2″,2″-dimethylchro-meno)-3′-prenylidihydrochalcone (1) together with 4-hydroxyonchocarpin (2), isobavachalcone (3), 4′,5-dihydroxy-6,7-(2,2-dimethyl-pyran)-2′-methoxy-8-γ,γ-dimethylallylflavone (4), artocarpin (5) and cycloheterophyllin (6) were successfully isolated from the leaves and heartwoods of *Artocarpus lowii* King (Moraceae). The structures of these compounds were fully characterised using spectroscopic methods and by direct comparison with published data. These compounds were tested for their antioxidant and tyrosinase inhibitory activities. Compound (1) displayed moderate antioxidant activity towards DPPH and tyrosinase inhibitory activities with SC50 value of 223.8 μM and IC50 value of 722.5 μM, respectively. Among the isolated compounds, cycloheterophyllin (6) showed the most potential antioxidant activity with SC50 value of 320.0 and 102.8 μM for ABTS and DPPH radicals scavenging activities, respectively, and also exhibited highest FRAP equivalent value of 4.7 ± 0.09 mM. Compound (6) showed tyrosinase inhibitory activity with the IC50 value of 104.6 μM.

**1. Introduction**

Moraceae is a family of flowering plants generally known as mulberry family. The family comprises 60 genera and approximately 1400 species that form a significant element in the
flora of the tropical region of South-East Asia. The most important genera are *Morus*, *Ficus* and *Artocarpus* which are widely used in the traditional medicines, economic source of food, agriculture and industry (Jarret 1959; Ng & Phil 1978). *Artocarpus* plants are widely investigated for their phytochemicals and bioactivities. Various new flavonoids had been successfully isolated from *Artocarpus* species especially chalcones, prenylated chalcones, prenylated flavones, geranylated flavones, flavanones and flavan-3-ols (Cao et al. 2003; Shen & Hou 2008; Ma et al. 2010; Ee et al. 2011; Jamil et al. 2012; Maneecai et al. 2012; Faiqah et al. 2013; Ren et al. 2013; Jin et al. 2015; Lathiff et al. 2015). A number of the isolated flavonoids showed interesting bioactivities including antioxidant (Jamil et al. 2008; Ee et al. 2011; Faiqah et al. 2013; Lin et al. 2015), cytotoxicity (Ma et al. 2010; Tantengco & Jacinto 2015), antimicrobial (Jayasinghe et al. 2004; Kuete et al. 2011; Jamil et al. 2014) and antityrosinase (Kuete et al. 2011; Najihah et al. 2012; Jin et al. 2015; Lathiff et al. 2015), antiviral (Likhitwitayawuid et al. 2005) and angiotensin-converting enzyme inhibitory activity (Siddesha et al. 2011). During our investigation for new and bioactive compounds from *Artocarpus* species, we have isolated new flavonoids with significant antioxidant and antimicrobial activities (Jamil et al. 2008; Lathiff et al. 2015). Further investigation on the leaves and heartwood of *Artocarpus lowii* has now led to the isolation of new dihydrochalcone 2′,4′-dihydroxy-3,4-(2,2′-dimethylchromeno)-3′-prenyldihydrochalcone (1) together with 4-hydroxycalconpin (2), isovachalcon (3), 4′,5-dihydroxy-6,7-(2,2-dimethylpyrano)-2′-methoxy-8-y,γ-dimethylallyflavone (4), arto- carpin (5) and cycloheterophyllin (6) (Figure 1). We report herein the isolation and structural elucidation of the new compound (1) together with the antioxidant and tyrosinase inhibitory activities of all compounds (1–6).

2. Results and discussion

Compound (1) was isolated as orange solid with m.p 95–97 °C from the MeOH crude extract of the leaves. The thin-layer chromatography (TLC) analysis gave a yellow spot after treated with vanillin sulphuric acid spraying reagent suggestive of a flavonoid-type structure. The IR spectrum showed broad absorption bands corresponded to chelated hydroxyl group and carbonyl group at 3310 and 1612 cm⁻¹, respectively. The UV maximum absorptions observed at 334, 263 and 240 nm in MeOH indicated a chalconoid structure. There was no bathochromic shift observed upon addition of NaOH suggesting that C-4 at B ring is substituted (Markam 1982). The molecular formula was determined to be C_{25}H_{28}O_{4} from its EIMS spectrum and was further supported by its HREIMS with molecular ion at m/z 392.1977 [M]+ (calculated for C_{25}H_{28}O_{4}, 392.1979). The ¹H NMR of (1) showed a characteristic signals for 2,2-dimethylchromeno group at δ 1.46 (6H, s, H-9″ and H-10″) and δ 5.73 (1H, d, J = 10.0 Hz, H-6″), δ 6.72 (1H, d, J = 10.0 Hz, H-7″) and a characteristic signals of a prenyl group at δ 1.73 (6H, s, H-4″ and H-5″); δ 3.34 (2H, d, J = 7.6 Hz, H-1″) and δ 5.32 (1H, t, J = 7.6 Hz, H-2″). An AB spin system was observed at δ 6.95 and δ 7.78 (2H, d, J = 8.6 Hz, H-5′ and H-6′) as well as an ABX spin system at δ 6.43 (1H, dd, J = 8.8 Hz and 2.4 Hz, H-6); δ 8.06 (1H, d, J = 8.8 Hz, H-5) and δ 6.35 (1H, d, J = 2.4 Hz, H-2). A singlet signal at downfield region δ 12.87 was attributable for a chelated hydroxyl group. Compound (1) was suggested as a dihydrochalcone by the presence of two triplets at δ 2.91 (2H, t, J = 7.6 Hz, H-α) and δ 3.22 (2H, t, J = 7.6 Hz, H-β). Analysis of the ¹³C NMR of (1) showed the presence of 25 carbons. DEPT spectrum showed the presence of four methyl carbons at δ 17.2 (C-5″), δ 25.0 (C-4″), δ 27.3 (C-10″) and δ 27.6 (C-9″). Structure of this dihydrochalcone was further confirmed by the presence of the
carbonyl carbon at higher chemical shift (δ 204.3) compared to other type of flavonoids and the absence of chemical shifts for H-α and H-β for typical chalcone (Faiqah et al. 2013). All proton/carbon signals and the position of the substituents on the aromatic rings were fully assigned on the basis of HMQC and HMBC spectral analysis. The HMBC correlations for H-1″/C-1′, C-2′ and C-5′ confirmed that the prenyl group was located at C-3′ of ring A. HMBC correlations of H-6″/C-3, C-4, H-7″/C-3, C-4 and H-2/C-3, C-4, C-7″ confirmed the linear type of 2,2-dimethylchromeno moiety in the structure (Figure S2). The NMR data of (1) were further compared with elastichalcone A isolated from A. elasticus (Faiqah et al. 2013). The molecular formula of (1) is the same as elastichalcone A but differ in the position of the substituent groups (Figure S3). Thus, compound (1) was deduced as 2′,4′-dihydroxy-3,4-(2″,2″-dimethylchromeno)-3′-prenylidihydrochalcone.

Structure determination for compounds (2–6) was based on extensive analysis of their spectral data and by comparison with literature values. Compound (2) was previously isolated from the leaves of A. lowii (Jamil et al. 2008), Glycyrrhiza glabra (Asada et al. 1998) and Dorstenia mannii (Ngadjui et al. 1992). Compound (3) was also found in the leaves of A. lowii (Jamil et al. 2008), G. glabra (Asada et al. 1998) and D. kameruniana (Abegaz et al. 1998). Compound (4) was isolated for the first time from A. anisophyllus (Lathiff et al. 2015) while compound (5) and (6) were found in A. heterophyllus (Rao et al. 1971; Lin et al. 1995).

Compounds (1–6) were tested for their antioxidant and tyrosinase inhibitory activities. The results for antioxidant and tyrosinase inhibitory activities are showed in Table 1. The antioxidant activity was evaluated using DPPH, ABTS and FRAP assays while the tyrosinase inhibitory activity (TIA) of all compounds was tested against mushroom tyrosinase. Butylated hydroxyanisole (BHA) and Trolox were used as the standard antioxidant while kojic acid was used as standard TIA. Compound (1) exhibited moderate antioxidant activity towards DPPH radicals and tyrosinase inhibitory activities with SC_{50} value of 223.8 μM and IC_{50} value of 722.5 μM, respectively. Compound (6) showed the most significant antioxidant activity by inhibiting DPPH and ABTS free radicals with SC_{50} values of 102.8 and 320.0 μM, respectively. Compound (6) also exhibited higher FRAP value (4.7 ± 0.09 mM) compared to other tested compounds. Compound (6) displayed significant tyrosinase inhibitory activity
against mushroom tyrosinase compared to the standard kojic acid (IC$_{50}$ = 219.6 μM). The presence of hydroxyl groups in the structure is responsible for antioxidant potentials and strongest radical absorption. The presence of 2,3-double bond in conjunction with 4-oxo function is also responsible for electron delocalisation (Lee et al. 2007). This study revealed that flavonoids isolated from A. lowii might be beneficial in the development of antioxidant and antityrosinase agents.

3. Experimental

3.1. General experimental procedures

Melting points were measured using melting point apparatus equipped with microscope, Leica Gallen III and were uncorrected. The IR spectra were recorded on Shimadzu Fourier Transform Infrared Spectrophotometer as thin film (NaCl windows) for liquid samples or KBr disc for solid samples. The Ultraviolet (UV) spectra were obtained on Shimadzu UV 1601PC spectrophotometer. The mass spectra were obtained from Mass Spectrometry Services, University College London, United Kingdom and National University of Singapore. The 1D and 2D NMR spectra were recorded in either deuterated chloroform or acetone on Bruker Avance 400 MHz Spectrometer, chemical shifts (δ) are reported in ppm on δ scale, and the coupling constants (J) are given in Hz. Vacuum liquid chromatography (VLC) was carried out on Merck silica gel 60 (230–400 mesh). Gravity column chromatography (CC) was performed on Merck silica gel 60 (70–230 mesh). Silica gel 60 F254 precoated aluminium sheets (0.20 mm, Merck) were used for TLC analysis of extracts, fractions and pure compounds. The TLC spots were visualised under UV light (254 and 365 nm) followed by spraying with 5% H$_2$SO$_4$ and 1% vanillin in MeOH and heating at 120°C for 5 min. All solvents were AR grade.

3.2. Plant material

The leaves and heartwoods of A. lowii were collected from Paka, Terengganu, Malaysia in September, 2010. A voucher specimen, AZ7094 was deposited at the Herbarium of Universiti Kebangsaan Malaysia, Bangi, Selangor.

Table 1. Antioxidant and tyrosinase inhibitory activities of compounds (1–6)

| Assays   | DPPH IC$_{50}$ (μM) | FRAP (mM equivalent to FeSO$_4$.7H$_2$O) | ABTS IC$_{50}$ (μM) | TIA IC$_{50}$ (μM) |
|----------|---------------------|----------------------------------------|---------------------|---------------------|
| Isolated compounds          |                     |                                        |                     |                     |
| (1)                        | 223.9               | –                                      | –                   | 722.5               |
| (2)                        | 279.0               | –                                      | –                   | 379.3               |
| (3)                        | 250.8               | 0.4 ± 0.05                             | 510.1               | 673.2               |
| (4)                        | 280.6               | –                                      | –                   | 720.1               |
| (5)                        | 344.5               | 0.2 ± 0.02                             | 400.1               | 722.5               |
| (6)                        | 102.8               | 4.7 ± 0.09                             | 320.0               | 104.6               |
| Standards                 |                     |                                        |                     |                     |
| BHA                       | 82.7                | 8.7 ± 0.42                             | 554.9               | –                   |
| Trolox                    | –                   | 2.8 ± 0.20                             | –                   | –                   |
| Kojic Acid                | –                   | –                                      | –                   | 219.6               |

Note: Results are expressed as mean ± SD of three replicates; ‘–’ not determined.
3.3. Extraction and isolation

Cold extraction of powdered leaves (2 kg) and heartwoods (1.8 kg) of *A. lowii* sequentially with *n*-hexane, CH$_2$Cl$_2$, and MeOH yielded the leaves crude extracts, *n*-hexane (ALLH: 9.4 g, 0.5%), CH$_2$Cl$_2$ (ALLD: 137.8 g, 6.7%), MeOH (ALLM: 120.9 g, 6.0%) and the heartwoods crude extracts, *n*-hexane (ALLH: 3.5 g, 0.2%), CH$_2$Cl$_2$ (ALHD: 43.7 g, 2.4%) and MeOH (ALHM: 78.9 g, 4.4%). The leaves MeOH extract (ALLM: 23.0 g) was subjected to VLC on silica gel, eluting with *n*-hexane, EtOAc and MeOH in order of increasing polarity followed by TLC analysis to give five major fractions, ALLM1–ALLM5. Fraction ALLM3 (6.0 g) was further purified by CC on silica gel using gradient solvent system of *n*-hexane-EtOAc (increased polarity by 3–5%) to yield compound (1) (42 mg). The leaves *n*-hexane extract (ALLH: 9.0 g) was fractionated by VLC on silica gel, eluting with *n*-hexane and EtOAc (increased polarity by 5%) followed by TLC analysis to afford six major fractions, ALLH1–ALLH6. Fraction ALLH4 (20.0 g) was also fractionated by silica gel VLC with solvent system of *n*-hexane and EtOAc (increased polarity by 10%) to afford four major fractions, ALLD1–ALLD4. Fraction ALLD4 (2.1 g) was purified by CC on silica gel eluted with combination of *n*-hexane-EtOAc (100:0 to 20:80) to yield compound (3) (45 mg). Similar CC purification on silica gel of the heartwoods *n*-hexane extract (ALHH: 3.0 g) eluting with combination of *n*-hexane and EtOAc (100:0 to 20:80) afforded compound (4) (45.3 mg). The heartwoods CH$_2$Cl$_2$ extract (ALHD: 20.0 g) was subjected to VLC on silica gel, eluting with solvent system of *n*-hexane and MeOH (up to 10% MeOH) followed by TLC analysis to give four major fractions, ALHD1–ALHD4. Fraction ALHD2 (5.0 g) was further purified by CC on silica gel, eluting using combination of *n*-hexane and EtOAc (100:0 to 10:90), followed by recrystallisation process to obtain compound (5) (1.1 g) and compound (6) (1.8 g). The heartwoods MeOH extract (ALHM: 20.0 g) was fractionated by VLC on silica gel with combination of *n*-hexane and EtOAc (increased polarity by 10%) and MeOH (up to 20% MeOH), followed by silica gel CC to afford more of compound (5) (1.8 g). Compounds (2–6) were deduced based on their spectral data and also by comparison with literature values.

3.3.1. 2′,4′-Dihydroxy-3,4-(2″,2″-dimethylchromeno)-3′-prenyldihydrochalcone (1)
Orange solids; m.p. 95–97 °C; UV (MeOH) λ$_{max}$ (log ε): 240 (0.93), 263 (0.80) and 334 (2.40) nm; IR (KBr) $\nu_{max}$ cm$^{-1}$: 3310, 2923, 2863, 1612, 1110; $^1$H NMR $\delta$ ppm (acetone-$d_4$, 400 MHz): 1.46 (6H, s, H-$9″$ and H-$10″$), 1.73 (6H, s, H-$4″$ and H-$5″$), 2.91 (2H, t, $J = 7.6$ Hz, H-$\alpha$), 3.22 (2H, t, $J = 7.6$ Hz, H-$\beta$), 3.34 (2H, d, $J = 7.6$ Hz, H-$1″$), 5.32 (1H, t, $J = 7.6$ Hz, H-$2″$), 5.73 (1H, d, $J = 10.0$ Hz, H-$6″$), 6.35 (1H, d, $J = 2.4$ Hz, H-$2$), 6.43 (1H, dd, $J = 8.8$ Hz and 2.4 Hz, H-$6$), 6.72 (1H, d, $J = 10.0$ Hz, H-$7″$), 6.95 (1H, d, $J = 8.6$ Hz, H-$5″$), 7.78 (1H, d, $J = 8.6$ Hz, H-$6″$), 8.06 (1H, d, $J = 8.8$ Hz, H-$5$), 12.87 (1H, s, 2″-OH); $^{13}$C NMR $\delta$ ppm (acetone-$d_4$, 100 MHz): 17.2 (CH$_3$), 25.0 (CH$_3$), 27.3 (CH$_3$), 27.6 (CH$_3$), 28.7 (CH$_2$), 29.8 (CH$_2$), 39.5 (CH$_2$), 77.5 (C), 102.8 (CH), 107.9 (CH), 108.3 (CH), 113.0 (C), 115.5 (C), 116.0 (CH), 117.2 (CH), 122.8 (CH), 126.6 (CH), 127.1 (C), 131.3 (CH), 131.9 (C), 133.3 (CH), 160.3 (C), 160.8 (C), 204.3 (C=O); COSY and HMBC see Table S2; HREIMS m/z 392.1977 [M$^+$] (calculated 392.1979 for C$_{25}$H$_{28}$O$_4$).
3.4. Biological activities

3.4.1. DPPH free radical scavenging assay
The free radical scavenging assay was conducted based on method described by Najihah et al. (2012) with minor modification. Detail of the protocol is provided as supplementary materials.

3.4.2. Ferric reducing antioxidant potential (FRAP) assay
The ferric reducing antioxidant potential (FRAP) assay was carried out according to Channarong et al. (2012) and Shahwar et al. (2012) with minor modification. Detail of the protocol is provided as supplementary materials.

3.4.3. 2,2′-Azinobis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) assay
The ABTS assay was conducted according to method described by Zou et al. (2011) with minor modification. Detail of the protocol is provided as supplementary materials.

3.4.4. Tyrosinase inhibitory activity
This assay was performed using method described by Kamkaen et al. (2007) and Likhitwitayawuid and Sritularak (2001) with minor modification. Detail of the protocol is provided as supplementary materials.

4. Conclusion
In this study, a new dihydrochalcone, 2′,4′-dihydroxy-3,4-(2″,2″-dimethylchromeno)-3′-prenylidihydrochalcone (1) and five known flavonoids were isolated from the leaves and heartwoods of A. lowii King. Their structures were characterised spectroscopically and by comparison with literature values. Compound (1) displayed moderate antioxidant activity towards DPPH and tyrosinase inhibitory activity with SC$_{50}$ value of 223.8 μM and IC$_{50}$ value of 722.5 μM, respectively. While compound (6) showed the most potential antioxidant activity towards DPPH with SC$_{50}$ value of 102.8 μM and exhibited highest FRAP equivalent value of 4.7 ± 0.09 mM. Compound (6) also showed significant tyrosinase inhibitory activity with IC$_{50}$ value of 104.6 μM.

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Disclosure statement
No potential conflict of interest was reported by the authors.

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