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Research Article

SOME FLAVONOIDS FROM LEAVES OF *ARTOCARPUS INTEGER* GROWING IN BINH PHUOC PROVINCE

Nguyen Thu Hoang Mai, Dang Minh Khai,
Tran Huu Phuoc, Nguyen Nam Phuong, Pham Duc Dung, Duong Thuc Huy*
Ho Chi Minh City University of Education, Vietnam
** Corresponding author: Duong Thuc Huy – Email: huydt@hcmue.edu.vn*
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ABSTRACT

*Artocarpus integer has been used as traditional medicine in Asian countries. This plant is common in Southern provinces of Vietnam, such as Binh Phuoc, Gia Lai, and Dong Nai. Investigation of the phytochemical of fruits of Artocarpus integer showed that flavonoid derivatives exhibited anti-inflammatory, antioxidant, antibacterial properties, and enzyme α-glucosidase inhibitions. This study isolated some compounds from ethyl acetate extract of leaves of Artocarpus integer. Four compounds including catechin (**1**), epi-catechin (**2**), (2S)-8-(3''-methylbut-2''-enyl)-7,3',4'-trihydroxyflavanone (**3**), and (2S)-liquiritigenin (**4**) were isolated from the ethyl acetate extract of Artocarpus integer leaves collected in Binh Phuoc Province. Their chemical structures were elucidated by comparing their spectroscopic data with reported data in the literature.*

Keywords: *Artocarpus integer;* flavonoid; flavanone; NMR spectroscopy

1. Introduction

Artocarpus integer (Thunb.) Merr. (Moraceae) is an edible evergreen fruit tree that grows in tropical and subtropical regions. In Vietnam, *Artocarpus integer* is grown in the southern provinces such as Binh Phuoc, Gia Lai, and Dong Nai (Do et al., 2004). It has ethnomedicine using as a malarial remedy, antipyretic, analgesic, laxative, constipation, diarrhea, diuretic, and anti-inflammatory (Mungmee et al., 2013). Its pulp and seeds are widely used as tonics for cooling and curing many diseases: root cures diarrhea and fever, and leaves stimulate breast milk in women (Jagtap et al., 2010). Recent investigations on the bioactive constituents of *A. integer* have reported the presence of flavonoid derivatives, some of which exhibited anti-inflammatory, antioxidant, and antibacterial properties and α-glucosidase inhibitions (Mungmee et al., 2013; Panthong et al., 2013). More recently, Duong et al. (2021) isolated 18 compounds from leaves of *A. integer* collected in Thailand,

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including flavonoids and phenolic compounds (Duong et al., 2021). Little is known about the phytochemical data of *A.integer*. This paper reported the isolations and structural elucidation of four flavanones from leaves of *A. integer* collected in Binh Phuoc Province, Vietnam.

2. Experiments

2.1. General experimental procedures

The NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz or 400 MHz for ^{1}H-NMR and 125 MHz or 100 MHz for ^{13}C-NMR) in acetone-d_6. Thin-layer chromatography was carried out on silica gel 60 (Merck, 40-63 μm), and spots were visualized by spraying with 10% H_2SO_4 solution, followed by heating.

2.2. Plant materials

Leaves of *Artocarpus integer* (L.) were collected in Binh Phuoc Province in August 2021. The scientific name of the material was identified as *Artocarpus integer* by Tran Cong Luan, Tay Do University, Vietnam. A voucher specimen (No UP-010) was deposited in the herbarium of the Department of Organic Chemistry, Faculty of Chemistry, Ho Chi Minh University of Education, Ho Chi Minh City, Vietnam.

2.3. Extraction and isolation

Dried leaves of *Artocarpus integer* (7 kg) were crushed and macerated with 20 L of MeOH (three times) at ambient temperature for eight h. The filtrated solution was evaporated to dryness under reduced pressure to obtain a crude extract (875 g). This crude extract was successively partitioned by *n*-hexane–EtOAc (1:1, v/v) and EtOAc to afford HEA (156.5 g) and EA (475 g) extracts, respectively. The EA extract was subjected to silica gel column chromatography (CC), eluted with the solvent system of *n*-hexane:ethyl acetate:acetone:methanol (10:1:1:0.01, v/v/v/v) to afford ten fractions EA1-EA10. Fraction EA1 (8.1 g) was applied to Sephadex LH-20 gel chromatography using methanol as a mobile phase to afford three fractions EA1.1-EA1.3. Fractions EA1.1 (3.2 g) was applied to silica gel column chromatography (CC), using the mixture of *n*-hexane: EtOAc: $CHCl_3$: acetone: H_2O (10:2:1:2:0.01, v/v/v/v/v) as a mobile phase to afford five fractions S1-S5. Fraction S1 (137 mg) was purified by silica gel CC, eluted with *n*-hexane: EtOAc: $CHCl_3$: acetone: H_2O (5:2:1:2:0.01, v/v/v/v/v) to afford compounds **3** (2.3 mg) and **4** (1.9 mg). Fraction EA2 (4.1 g) was applied to silica gel column chromatography (CC), eluted with *n*-hexane: EtOAc: $CHCl_3$: acetone: H_2O (5:2:1:2:0.01, v/v/v/v/v) to give five fractions EA2.1-2.5. Purifying fraction EA2.1 (412 mg) by silica gel CC, using the same mobile phase as described previously, resulted in compounds **1** (31 mg) and **2** (25 mg).

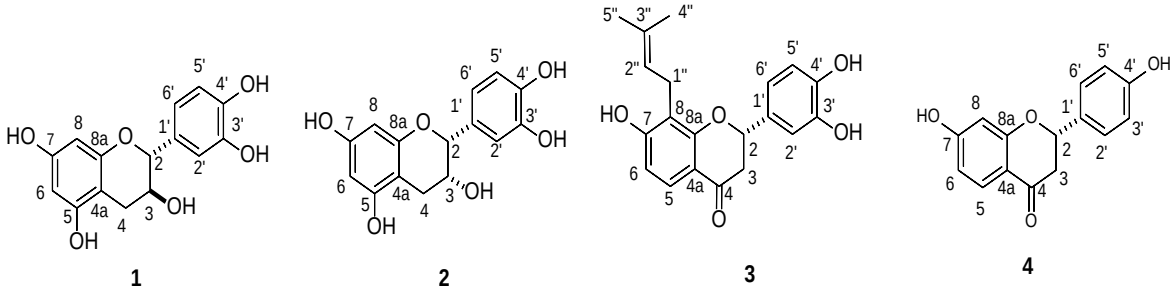

Figure 1. *Chemical structures of isolated compounds* ***1-4***

● **Catechin** (**1**). White amorphous solid. ^{1}H-NMR (400 MHz, acetone-d_6, ppm, J in Hertz): δ 4.54 (1H, d, 8.2 Hz, H-2), 3.98 (1H, ddd, 8.5, 8.2, 5.5, H-3), 2.52 (1H, dd, 16.0, 8.5, H-4ax), 2.91 (1H, dd, 16.0, 5.5, H-4eq), 6.03 (1H, d, 2.3, H-6), 5.87 (1H, d, 2.3, H-8), 6.90 (1H, d, 1.8, H-2'), 6.80 (1H, d, 8.0, H-5'), 6.75 (1H, dd, 1.8, 8.0 H-6'). ^{13}C-NMR (100 MHz, acetone-d_6, ppm): δ 82.9 (C-2), 68.9 (C-3), 28.6 (C-4), 100.9 (C-4a), 157.9 (C-5), 96.4 (C-6), 157.6 (C-7), 95.6 (C-8), 157.0 (C-8a), 132.3 (C-1'), 116.1 (C-2'), 146.3 (C-3'), 146.3 (C-4'), 115.3 (C-5'), 120.1 (C-6') (Davis et al., 1996).

● **Epi-catechin** (**2**). White amorphous solid. ^{1}H-NMR (400 MHz, acetone-d_6, ppm, J in Hertz): δ 4.85 (1H, s, H-2), 4.18 (1H, dd, 4.5, 3.4, H-3), 2.83 (1H, dd, 16.6, 4.5, H-4ax), 2.70 (1H, dd, 16.6, 3.4, H-4eq), 5.99 (1H, d, 1.8, H-6), 5.88 (1H, d, 1.8, H-8), 7.01 (1H, d, 1.8, H-2'), 6.75 (1H, d, 8.0, H-5'), 6.80 (1H, dd, 8.0, 1.8, H-6'). ^{13}C-NMR (100 MHz, acetone-d_6, ppm): δ 79.6 (C-2), 67.1 (C-3), 29.2 (C-4), 100.0 (C-4a), 157.8 (C-5), 96.3 (C-6), 157.8 (C-7), 95.5 (C-8), 157.4 (C-8a), 132.5 (C-1'), 115.5 (C-2'), 145.6 (C-3'), 145.5 (C-4'), 115.7 (C-5'), 129.6 (C-6') (Davis et al., 1996).

● **(2*S*)-8-(3''-methylbut-2''-enyl)-7,3',4'-trihydroxyflavanone (3).** $[\alpha]_D^{25}$ -428 (*c* 0.1, MeOH). Yellow amorphous powder. ^{1}H NMR (500 MHz, acetone-d_6, ppm, J/Hz): δ 7.60 (1H, d, 8.5, H-5), 7.37 (1H, d, 8.0, H-2'), 6.61 (1H, d, 8.5, H-6), 6.45 (1H, d, 2.5, H-6'), 6.44 (1H, dd, 8.0, 2.5, H-5'), 5.69 (1H, dd, 13.5, 3.0, H-2), 5.26 (1H, t, 6.5, H-2''), 3.35 (2H, m, H-1''), 2.96 (1H, dd, 16.5, 13.0, H-3a), 2.71 (1H, dd, 16.5, 3.0, H-3b), 1.65 (3H, s, H-5''), 1.61 (3H, s, H-4'') (Uriburu et al., 2007).

● **(2*S*)-*Liquiritigenin*** (**4**)**.** Yellow amorphous powder. 1H NMR (500 MHz, acetone-d_6, ppm, J/Hz): δ 7.72 (1H, d, 8.5, H-5), 7.40 (2H, d, 8.0, H-2', H-6'), 6.90 (2H, d, 8.0, H-3', H-5'), 6.57 (1H, dd, 8.5, 2.5, H-6), 6.42 (1H, d, 2.0, H-8), 5.45 (1H, dd, 13.0, 2.5, H-2), 3.05 (1H, dd, 16.5, 13.0 , H-3a), 2.67 (1H, dd, 16.5, 3.0, H-3b) (Lee et al., 2021).

3. Results and discussion

Compound **1** was obtained as a white amorphous solid. The ^{1}H NMR spectrum of **1** exhibited two aromatic protons of a 1,2,3,5-tetrasubstitutedbenzene ring [δ 6.03 (1H, d, 2.3, H-6), 5.87 (1H, d, 2.3, H-8)], three aromatic protons of a 1,2,4-trisubsitutedbenzene ring [δ 6.90 (1H, d, 1.8, H-2'), 6.80 (1H, d, 8.0, H-5'), 6.75 (1H, dd, 1.8, 8.0 H-6')], two oxymethines at δ_H 4.54 (1H, d, 8.2, H-2) and 3.98 (1H, ddd, 8.5, 8.2, 5.5, H-3), a methylene at δ_H 2.52 (1H, dd, 16.0, 8.5, H-4ax) and 2.91 (1H, dd, 16.0, 5.5, H-4eq). The ^{13}C-NMR spectrum showed 12 aromatic carbons at δ_C 132.3 (C-1'), 116.1 (C-2'), 146.3 (C-3'), 146.3 (C-4'), 115.3 (C-5'), 120.1 (C-6'), 100.9 (C-4a), 157.9 (C-5), 96.4 (C-6), 157.6 (C-7), 95.6 (C-8), 157.0 (C-8a) and three sp^3 carbons at δ_C 79.6 (C-2), 67.1 (C-3), 29.2 (C-4). NMR data of **1** were consistent with those of catechin (Davis et al., 1996). Thus, **1** was elucidated as catechin.

Compound **2** was obtained as a white amorphous powder. Comparison of NMR data of **1** and **2** gave high similarity, indicating that they shared the same planar structure. The differences are the chemical shifts of CH-2/CH-3/CH_2-4. This indicated that **2** was an epimer of **1** with the change of configuration of C-3. The small *J* value of H-2 and H-3 indicated the cis conjunction of these two protons. NMR data of **2** was consistent with those of epi-catechin (Davis et al., 1996). Thus, **2** was elucidated as epi-catechin.

Compound **3** was obtained as a yellow solid. The ^{1}H NMR spectrum of **3** exhibited five aromatic protons characteristic of a 1,2,3,4-tetrasubsitutedbenzene ring [δ_H 7.60 (1H, d, 8.5, H-5) and 6.61 (1H, d, 8.5, H-6)] and a 1,2,4-trisubstitutedbenzen ring [δ_H 7.37 (1H, d, 8.0, H-2'), 6.47 (1H, d, 2.5, H-6'), 6.44 (1H, dd, 8.0, 2.5, H-5')]. In addition, ^{1}H NMR spectrum showed an ABX system including one oxymethine at δ_H 5.69 (1H, dd, 13.5, 3.0, H-2) coupled with one methylene at δ_H 2.96 (1H, dd,16.5,13.0, H-3a) and 2.71 (1H, dd, 16.5,3.0, H-3b) and an isoprenyl chain [δ_H 3.35 (2H, brd, 6.5, H-1''), 5.26 (1H, brt, 6.5, H-2''), 1.65 (3H, br s, H-5''), and 1.61 (3H, br s, H-4'')]. NMR data of **3** were consistent with those of 8-(3''-methylbut-2''-enyl)-7,3',4'-trihydroxyflavanone (Uriburu et al., 2007). Thus **3** was elucidated as 8-(3"-methylbut-2"-enyl)-7,3',4'-trihydroxyflavanone. The absolute configuration of C-2 was defined by the negative optical rotation of **3** (Uriburu et al., 2007).

Compound **4** was obtained as a yellow amorphous powder. Comparison of NMR data of **4** and **3** gave high similarity, indicating that they shared the same structure. The differences are the replacements of an isoprenyl chain for H-8 [δ_H 6.42 (1H, d, 2.0, H-8)] and of a hydroxy group for H-3' position [δ_H 6.90 (2H, d, 8.0)] in **4**. NMR data of **4** was consistent with those of (2S)-liquiritigenin. Thus **4** was elucidated as (*2S*)-liquiritigenin (Lee et al., 2021).

4. Conclusions

From leaves of *Artocarpus integer* collected in Binh Phuoc Province, four flavanols catechin (**1**), epi-catechin (**2**), (2*S*)-8-(3"-methylbut-2"-enyl)-7,3',4'-trihydroxyflavanone (**3**), (2*S*)-liquiritigenin (4) were isolated. Their chemical structures were determined by using NMR spectroscopic methods as well as comparison with the literature. All compounds were previously reported from this species, but they were reported for the first time from the Vietnamese species.

❖ ***Conflict of Interest:*** *Authors have no conflict of interest to declare.*

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MỘT SỐ FLAVONOID TỪ LÁ CÂY MÍT TỐ NỮ *ARTOCARPUS INTEGER* THU HÁI Ở TỈNH BÌNH PHƯỚC

Nguyễn Thu Hoàng Mai, Đặng Minh Khải,
Trần Hữu Phước, Nguyễn Nam Phương, Phạm Đức Dũng, Dương Thúc Huy*
Trường Đại học Sư phạm Thành phố Hồ Chí Minh, Việt Nam
**Tác giả liên hệ: Dương Thúc Huy – Email: huydt@hcmue.edu.vn*
Ngày nhận bài: 29-3-2023; ngày nhận bài sửa: 19-4-2023; ngày duyệt đăng: 11-5-2023

TÓM TẮT

*Artocarpus integer được sử dụng trong y học cổ truyền ở nhiều nước châu Á. Artocarpus integer là loài cây phổ biến ở các tỉnh miền Nam Việt Nam như Bình Phước, Gia Lai và Đồng Nai. Nghiên cứu về thành phần hóa học của lá cây mít tố nữ Artocarpus integer cho thấy những dẫn xuất của flavonoid có những hoạt tinh sinh học như kháng viêm, kháng oxi hóa, kháng khuẩn và ức chế enzyme α-glucosidase. Đề tài đã nghiên cứu phân lập một số hợp chất từ cao chiết ethyl acetate của lá cây mít tố nữ Artocarpus integer. Bốn hợp chất bao gồm catechin (**1**), epi-catechin (**2**), (2S)-8-(3''-methylbut-2''-enyl)-7,3',4'-trihydroxyflavanone (**3**) và (2S)-liquiritigenin (**4**) được phân lập từ cao ethyl acetate của lá cây mít tố nữ thu hái tại tỉnh Bình Phước bằng các phương pháp sắc kí. Cấu trúc hóa học của các hợp chất được xác định bằng các phương pháp phổ cộng hưởng từ hạt nhân đồng thời so sánh với các dữ liệu phổ trong tài liệu tham khảo.*

Từ khóa: *Artocarpus integer;* flavonoid; flavanone; NMR spectroscopy