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), epicatechin (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\(_2\)SO\(_4\) 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\(_2\)O (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\(_2\)O (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\(_2\)O (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): $\delta$ 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, d, 1.8, 8.0 H-6'). $^{13}$C-NMR (100 MHz, acetone-$d_6$, ppm): $\delta$ 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., n.d.).

- **Epi-catechin** (2). White amorphous solid. $^1$H-NMR (400 MHz, acetone-$d_6$, ppm, J in Hertz): $\delta$ 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, d, 8.0, 1.8, H-6'). $^{13}$C-NMR (100 MHz, acetone-$d_6$, ppm): $\delta$ 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., n.d.).

- **(2S)-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): $\delta$ 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).

- **(2S)-Liquiritigenin (4).** Yellow amorphous powder. 1H NMR (500 MHz, acetone-$d_6$, ppm, J/Hz): $\delta$ 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 [$\delta$ 6.03 (1H, d, 2.3, H-6), 5.87 (1H, d, 2.3, H-8)], three aromatic protons of a 1,2,4-trisubstitutedbenzene ring [$\delta$ 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 $\delta$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 $\delta$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 $\delta$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 sp3 carbons at $\delta$C 79.6 (C-2), 67.1 (C-3), 29.2 (C-4). NMR data of 1 were consistent with those of catechin [6]. 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/CH2-4. 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 [6]. 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-tetrasubstitutedbenzene ring [$\delta$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 [\(\delta\)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 $\delta$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 [\(\delta\)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 [\(\delta\)H 6.42 (1H, d, 2.0, H-8)] and of a hydroxy group for H-3' position [\(\delta\)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).\)

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4. Conclusions

From leaves of *Artocarpus integer* collected in Binh Phuoc Province, four flavanols catechin (1), epi-catechin (2), (2S)-8-(3''-methylbut-2''-enyl)-7,3',4'-tri hydroxyflavanone (3), (2S)-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.

REFERENCES


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

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TÓM TẮT

Artocarpus integer được sử dụng trong y học cổ truyền ở nhiều nước châu Á. Artocarpus integer là loại 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 tộ nữ Artocarpus integer cho thấy những dẫn xuất của flavonoid có những hoạt tính 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 tộ 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 tộ nữ thu hái tại tỉnh Bình Phước bằng các phương pháp sắc ký. Cấu trúc hóa học của các hợp chất được xác định bằng các phương pháp phổ có công 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