ISOLATION AND STRUCTURE ELUCIDATION OF *ENT*-KAURANE COMPOUNDS FROM THE MESOCARP OF *ANNONA GLABRA* L.

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TÓM TẮT

PHÂN LẬP VÀ XÁC ĐỊNH CẤU TRÚC CÁC HỢP CHẤT *ENT*-KAURANE TỪ THỊT QUẢ CỦA CÂY BÌNH BÁT NƯỚC *ANNONA GLABRA* L.

Từ dịch chiết điều chế từ phần thịt quả của cây Bình bát nước (Annona glabra L.), một số hợp chất diterpenoid thuộc khung ent-kaurane đã được phân lập, bao gồm: 16□-H-ent-kaurane-17-oic acid (1), 16□-H-ent-kaurane-17,19-dioic acid (2), ent-kaurane-16-en-19-ol (3), 16□-H-ent-kaurane-17,18-dioic acid, 17-methyl ester (4), và 16□ı□-dihydroxykauran-19-oic acid (5). Cấu trúc của các hợp chất được thực hiện thông qua các phương pháp phân tích phổ, kết hợp với đối chiếu dữ liệu phổ đã được công bố. Đáng chú ý, đây là lần đầu tiên hợp chất 16□-H-ent-kaurane-17-oic acid (1) được báo cáo phân lập từ loài Bình bát nước Annona glabra L.

Từ khóa: *Annona glabra, diterpenoid, ent-kaurane.*

1. INTRODUCTION

Medicinal plants are a rich source of bioactive natural compounds which are highly regarded for their potent efficacy, abundant availability, and practical utility [1]. Throughout medicinal history, numerous plants have been recognized and utilized by our ancestors as primary remedies for a wide range of health conditions [2]. Annonaceae, a major family within the Magnollidae subclass, includes nearly 2,400 species in 108 genera and is mainly distributed across pantropical areas [3]. *Annona glabra* L., also known as Pond apple, is a native wild tree from the *Annona* genus of Annonaceae family. It is an invasive plant species widely distributed in tropical and subtropical regions with high adaptability, rapid dispersal, and prolific reproduction [4]. In Asian countries like the Maldives, the fruit is a popular ingredient in beverages or fresh juices. In traditional medicine, crushed seeds boiled with coconut oil are also employed to treat lice infestations [5]. The young leaves and stems of *A. glabra*, when combined with *Passiflora foetida* leaves and stems, can be brewed into an anthelmintic tea effective against helminths and nematodes. Additionally, other vegetative parts of *A. glabra* such as roots and mature stems possess significant medicinal value. These are traditionally used to treat fever, constipation, and cardiovascular support, and act as a sedative in folk medicine [6]. Research on *A. glabra* stem, pulp, leaves, root, seed and fruit extracts has identified various classes of natural compounds, including flavonoids, glycosides, saponins, tannins, steroids, organic acids, anthraquinones, and alkaloids, showing many biological activities such as anti-HIV (in lymphocyte replication), cytotoxic, trypanocidal, larvicidal, antimicrobial, vermifuge, contraceptive and anti-*Leishmania* effects [7, 8]. Particularly, certain alkaloids isolated from this species have been demonstrated to possess significant anti-*Leishmania* activity [9]. Furthermore, the isolated acetogenins have emerged as promising candidates for leishmanicidal applications, while kaurenoic acid has shown noteworthy activity against *Trypanosoma cruzi* and HIV, along with broad-spectrum antimicrobial effects [6, 9]. However, current research on the fruit pulp of *A. glabra* remains limited, and the use of the whole fruits (including seeds) in many studies can lead to misunderstanding in the phytochemicals of the fruit pulp, motivating the present investigation. This study successfully extracted and isolated five compounds from *Annona glabra* pulp:16□-H-*ent*-kaurane-17-oic acid (**1**), 16□-H-*ent*-kaurane-17,19-dioic acid (**2**), *ent*-kaurane-16-en-19-ol (**3**), 16□-H-*ent*-kaurane-17,18-dioic acid, 17-methyl ester (**4**), 16□,17-dihydroxykauran-19-oic acid (**5**). The structures of these compounds were determined through comprehensive spectroscopic analysis, together with literature comparisons.

2. MATERIAL AND METHODS

2.1 Plants materials

The fruit of *A. glabra* were gathered in Long Binh Ward, Thu Duc City, Ho Chi Minh City, Vietnam in September 2023, whose taxonomy identification was accomplished by Dr. Dang Van Son, Vietnam Academy of Science and Technology, Institute of Tropical Biology, Ho Chi Minh City, Vietnam. The voucher specimen (No. AG001) was preserved at the Future Materials and Devices Laboratory (FM&D Lab), Institute of Fundamental and Applied Sciences (IFAS), Duy Tan University, Ho Chi Minh City, Vietnam.

2.2 General experimental procedures

NMR spectra were obtained using a Bruker Avance spectrometer at 600 MHz for ^{1}H-NMR and 150 MHz for ^{13}C-NMR, with tetramethylsilane (TMS) as the internal reference standard. Chemical shifts are reported in parts per million (ppm). Column chromatography (CC) was carried out using silica gel (0.04 – 0.06 mm, 240 – 430 mesh, Merck) and reversed-phase silica gel (RP-18, 0.03 –

0.05 mm). For thin-layer chromatography (TLC), precoated plates of Kieselgel 60 F_{254} or 60 RP-18 F_{254s} were employed. Visualization of separated compounds on TLC was performed under UV light at 254 nm and/or by spraying with 10% H_2SO_4 in ethanol, followed by heating.

2.3 Extraction and isolation

Air-dried pulp obtained from *A. glabra* fruit (1.0 kg) was introduced to the Soxhlet extraction system. After the successive extraction using four solvents of increasing polarity, the filtered solution was then concentrated *in vacuo* to yield four respective extracts: **BBH** (*n*-hexane), **BBDc** (dichloromethane), **BBEa** (ethyl acetate), and **BBEt** (ethanol). Fractionation of the *n*-hexane extract (**BBH**, 146.7 g) was carried out as follows. **BBH** was subjected to normal-phase silica gel CC using *n*-hexane:dichloromethane (6:4, v/v) solvent system to give eight fractions (**H1-H8**). Fractions **H1** (39.2 g) and **H2** (41.7 g) underwent reversed-phase silica gel chromatography with a methanol:H_2O (5:0.5, v/v) solvent system, resulting in subfractions **H1.1–H1.6** and **H2.1–H2.5**, respectively. Subsequent purification of fraction H1.1 (11.6 g) via normal-phase silica gel column chromatography using an *n*-hexane:dichloromethane:methanol (10.0:10.0:0.5, v/v/v) mixture yielded four subfractions (**H1.1.1–H1.1.4**). Subfraction **H1.1.2** (3.1 g) was chromatographed under the same conditions to yield compound **4** (7.6 mg). Fraction **H1.1.3** (5.1 g) was further purified by normal-phase chromatography, eluted with *n*-hexane:dichloromethane:methanol (4.5:3:0.3, v/v/v), to afford compound **1** (3.0 mg) and **2** (4.9 mg).

Fraction **H2.**1 (13.3 g) was further purified by normal-phase silica gel column chromatography with an *n*-hexane:dichloromethane (7:1, v/v) solvent system, producing six subfractions (**H2.1.1–H2.1.6**). Subfraction **H2.1.3** (4.4 g) underwent additional normal-phase silica gel column chromatography using an *n*-hexane:dichloromethane:methanol (2.5:2.5:0.3, v/v/v) solvent system, yielding compound **3** (4.5 mg). Similarly, fraction **H2.1.4** (2.1 g) was purified by normal-phase silica gel CC with a *n*-hexane:dichloromethane:methanol (2.5:3.0:0.25, v/v/v) eluent to yield compound **5** (4.2 mg).

Compound 1 (16□-H-*ent*-kaurane-17-oic acid): White amorphous powder. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ_H 2.94 (1H, *dt*, *J* = 6.0, 12.0 Hz, H-16), 2.57 (1H, *brs*, H-13), 0.99 (3H, *s*, H-20), 0.84 (3H, *s*, H-19), 0.80 (3H, *s*, H-18); and ^{13}C-NMR ($CDCl_3$, 150 MHz): see Table 1.

Compound 2 (16□-H-*ent*-kaurane-17,19-dioic acid): White amorphous powder. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ_H 2.83 (1H, *m*, H-16), 1.93 (1H, *d*, *J* = 12.9 Hz, H-13), 1.10 (3H, *s*, H-18), 0.86 (3H, *s*, H-20); and ^{13}C-NMR (DMSO-d_6, 150 MHz): see Table 1.

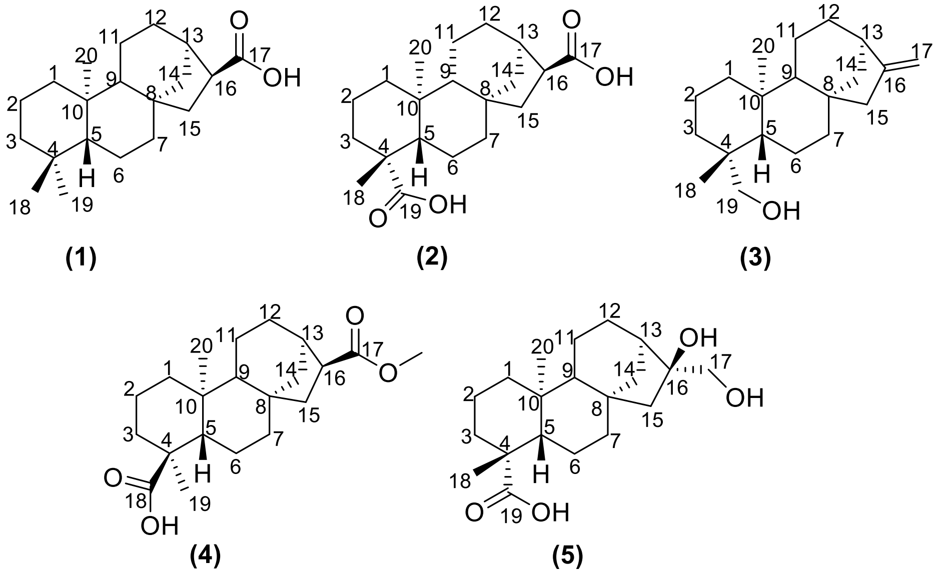
Compound 3 (*ent*-kaurane-16-en-19-ol): White amorphous powder. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ_H 4.79 (1H, *brs*, H-17a), 4.73 (1H, *brs*, H-17b), 3.74 (1H, *d*, *J* = 11.4 Hz, H-18a), 3.45 (1H, *d*, *J* = 11.4 Hz, H-18b), 2.63 (1H, *brs*, H-13), 2.05 (2H, *m*, H-15), 1.01 (3H, *s*, H-20), 0.96 (3H, *s*, H-18); and ^{13}C-NMR ($CDCl_3$, 150 MHz): see Table 1.

Compound 4 (16□-H-*ent*-kaurane-17,18-dioic acid, 17-methyl ester): White amorphous powder. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ_H 3.69 (3H, *s*, 17-OCH_3), 2.88 (1H, *m*, H-16), 0.92 (3H, *s*, H-20), 2.51 (1H, *brs*, H-13), 1.23 (3H, *s*, H-19); and ^{13}C-NMR ($CDCl_3$, 150 MHz): see Table 1.

Compound 5 (16□,17-dihydroxykauran-19-oic acid): White amorphous powder. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ_H 3.49 (1H, *d*, *J* = 11.4 Hz, H-17a), 3.39 (1H, *d*, *J* = 11.4 Hz, H-17b), 1.99 (1H, *d*, *J* = 13.8 Hz, H-13), 1.08 (3H, *s*, H-19), 0.87 (3H, *s*, H-20); and ^{13}C-NMR (DMSO-d_6, 150 MHz): see Table 1.

3. RESULTS AND DISCUSSIONS

From the *n*-hexane extract of *A. glabra*, five *ent*-kaurane diterpenoids (**1-5**) were isolated through phytochemical investigation, as shown in Figure 1.



(1) (2) (3)

(4) (5)

Figure 1. *Chemical structures of isolated compounds from A. glabra.*

Compound **1** was a white amorphous powder. The analysis of ^{1}H-NMR spectrum indicated the presence of notable signals, including three methyl groups at δ_H 0.80 (3H, *s*, H-19), 0.84 (3H, *s*, H-18), 0.99 (3H, *s*, H-20), two methine protons at δ_H 2.94 (1H, *dt*, *J* = 6.0, 12.0 Hz, H-16), 2.57 (1H, *brs*, H-13), and several proton resonances were observed in the upfield region between δ_H 1.90 – 0.72. On the ^{13}C-NMR spectrum of **1**, signals of 20 carbons were observed, including one carbonyl carbon resonance at δ_C 182.1 (C-17), nine methylene carbon signals at δ_C 18.8 (C-11), 20.6 (C-6), 27.6 (C-12), 39.5 (C-3), 40.9 (C-1), 41.8 (C-7), 42.0 (C-14), 42.2 (C-15), and 18.1 (C-2), three quaternary carbon signals at δ_C 44.6 (C-8), 40.0 (C-10), and 33.4 (C-4), three methyl carbon signals at δ_C 33.8 (C-18), 21.8 (C-19), and 17.8 (C-20); and four methine carbon signals at δ_C 57.3 (C-9), 56.4 (C-5), 45.5 (C-16), and 40.5 (C-13). The analysis of these spectroscopic data suggested **1** with the structure of an *ent*-kaurane diterpenoid, which showed a good fit with those of 16□-H-*ent*-kaurane-17-oic acid [10]. Accordingly, compound **1** was characterized and assigned the structure of 16□-H-*ent*-kaurane-17-oic acid.

Compound **2** was a white amorphous powder. The ^{1}H-NMR spectrum of the compound exhibited the presence of two methyl protons at δ_H 1.10 (3H, *s*, H-18), 0.86 (3H, *s*, H-20), two methine protons at δ_H 2.83 (1H, *m*, H-16), 1.93 (1H, *d*, *J* = 12.9 Hz, H-13), and several proton signals were presented at the range of δ_H 1.78 – 0.76. Further analysis on its ^{13}C-NMR spectrum displayed 20 carbon signals, including two carboxyl carbons at δ_C 178.8 (C-19) and 175.5 (C-17); nine saturated methylene carbons at δ_C 41.6 (C-14), 41.2 (C-15), 40.2 (C-3), 40.0 (C-7), 37.6 (C-1), 27.1 (C-12), 21.9 (C-6), 18.8 (C-2), and 17.8 (C-11), three quaternary carbons at δ_C 43.9 (C-8), 42.8 (C-4), and 39.1 (C-10), and two methyl carbons δ_C 28.6 (C-18) and 15.3 (C-20). Four methine carbon signals were recorded at δ_C 56.0 (C-5), 55.7 (C-9), 44.9 (C-16), and 38.7 (C-13). In comparison with the NMR data of compound **1**, the 1D NMR data of **2** exhibited similar to those of **1**, an *ent*-kaurane diterpenoid, except for the lack of one methyl proton (δ_H 0.84, H_3-19) along with the occurrence of a carboxylic acid (-COOH) at δ_C 178.8 (C-19) located at C-4, further supported by the chemical shift of C-4 carbon at δ_C 42.8 (instead of δ_C 33.4, in **1**). Further comparison with the spectral data of 16□-H-*ent*-kaurane-17,19-dioic acid [11] revealed a high similarity, thereby confirming compound **2** as 16□-H-*ent*-kaurane-17,19-dioic acid.

Compound **3** was a white amorphous powder. In comparison with the NMR data depicted from **1** and **2**, the structure of **3** as an *ent*-kaurane diterpenoid was confirmed. In particular, the appearance of two *gem*-olefin proton at δ_H 4.79 (1H, *brs*, H-17a), 4.73 (1H, *brs*, H-17b), along with the lack of one methine proton H-16, indicated the presence of a C=C double bond at C-16/17. This was further supported by the presence of a tertiary olefin carbon at δ_C 156.1 (C-16) instead of δ_C 45.5 (C-16 in **1**). Moreover, the appearance of oxymethylene protons at δ_H 3.74 and 3.44, and the absence of a methyl group indicated the replacement of a $-CH_2OH$ for a methyl proton H_3-19 (δ_H 0.84 in **1**). As the suggested structure of **3** and its NMR data fit well to those reported for *ent*-kaurane-16-en-19-ol [12], **3** was identified.

Compound **4** was also isolated as a white amorphous powder. The ^{1}H-NMR spectrum of the compound showed characteristic signals for two methyl protons at δ_H 0.92 (3H, *s*, H-20), 1.23 (3H, *s*, H-19), one methoxy proton at δ_H 3.69 (3H, *s*, 17-OCH_3), one methylene proton at δ_H 1.52 (2H, *m*, H-15), two methine proton at δ_H 2.88 (1H, *m*, H-16), 2.57 (1H, *brs*, H-13), and several protons in the range of δ_H 2.15 - 0.80. The ^{13}C-NMR spectrum of compound **4** revealed 21 carbon signals, with two carbonyl carbons observed at δ_C 183.7 (C-18) and 175.4 (C-17); nine methylene carbons at δ_C 42.0, 41.9, 40.7, 40.7, 38.0, 27.7, 22.2, 19.2, and 18.3; three quaternary carbons at δ_C 44.5, 43.8, and 39.8; two methyl carbons at δ_C 29.1 and 15.7; four methine carbons at δ_C 57.1, 56.3, 45.6, and 39.8; one methoxy carbon at δ_C 51.6. In comparison with the NMR data depicted from **1, 2** and **3**, the structure of **4** as an *ent*-kaurane diterpenoid. The ^{1}H and ^{13}C-NMR spectra of **4** exhibited similar signals to those of **1**, except for the appearance of one more methoxy group (17-OCH_3) at δ_H 3.69 and δ_C 51.6 indicating the presence of a methyl ester at the C-16. Besides, the lack of a methyl group at the C-4 along with the presence of a carboxyl carbon at δ_C 183.7 suggested the occurrence of a carboxylic acid group located at C-4. Further comparison of the NMR data of **4** with those reported for 16□-H-*ent*-kaurane-17,18-dioic acid, 17-methyl ester [13] showed significant similarity, hence indicating **4** as 16□-H-*ent*-kaurane-17,18-dioic acid, 17-methyl ester.

Compound **5** was a white amorphous powder. The analysis of ^{1}H-NMR spectrum indicated the presence of notable signals, including two methyl protons at δ_H 1.08 (3H, *s*, H-18), 0.87 (3H, *s*, H-20), two protons of oxymethylene at δ_H 3.49 (1H, *d*, *J* = 11.4 Hz, H-17a) and 3.39 (1H, *d*, *J* = 11.4 Hz, H-17b), and several proton signals were appeared in the upfield region between δ 2.15 – 0.80 ppm. Further elucidation based on ^{13}C-NMR spectrum displayed **5** with a 20-carbon structure, containing one carbonyl carbon at δ_C 178.7 (C-19), nine methylene carbons at δ_C 18.1 (C-2), 18.8 (C-11), 22.0 (C-6), 25.8 (C-12), 36.7 (C-14), 37.7 (C-3), 41.9 (C-7), 42.8 (C-1), 52.8 (C-15); one oxygenated methylene carbon at δ_C 65.3 (C-17), three quaternary carbons at δ_C 44.5 (C-4), 44.0 (C-8), 39.1 (C-10), one oxygenated quaternary carbon at δ_C 80.5 (C-16); three methine carbons at δ_C 56.0 (C-5), 55.4 (C-9), 40.2 (C-13), two methyl carbons at δ_C 28.6 (C-18), 15.4 (C-20). In comparison with the NMR data depicted from **1**, **2**, **3** and **4**, the structure of **5** as an *ent*-kaurane diterpenoid. A comparative analysis of the spectral data with compound **2** indicated certain structural discrepancies. In particular, the presence of a carboxyl carbon signal at δ_C 178.7 indicates a carboxylic acid group (-COOH) directly attached at the C-4 position. Besides, the presence of two oxymethylene protons at δ_H 3.49 (1H, *d, J* = 11.4 Hz, H-17a), 3.39 (1H, *d*, *J* = 11.4 Hz, H-17b) determined the occurrence of a hydroxymethylene (-CH_2OH) located at an oxygenated tertiary carbon C-16 (δ_C 80.5). Furthermore, the 1D NMR data of **5** was further compared to those reported for 16□ı□-dihydroxykauran-19-oic acid [14, 15], showing a good fit and confirming **5** as 16□ı□-dihydroxykauran-19-oic acid.

Table 1: *^{13}C-NMR spectral data of compounds **1-5** and references.*

C	1		2		3		4		5	
	$\delta_C{}^{a,d}$	$\delta_C{}^{a,f}$ [10]	$\delta_C{}^{b,d}$	$\delta_C{}^{b,e}$ [11]	$\delta_C{}^{a,d}$	$\delta_C{}^{a,e}$ [12]	$\delta_C{}^{a,d}$	$\delta_C{}^{a,f}$ [13]	$\delta_C{}^{b,d}$	$\delta_C{}^{c,f}$ [15]
1	40.9	40.4	37.6	38.1	40.6	40.5	40.7	40.8	42.8	41.8
2	18.1	18.0	18.8	19.3	18.5	18.3	18.3	18.7	18.1	19.0
3	39.5	39.0	40.2	40.6	35.8	35.6	38.0	37.9	37.7	38.0
4	33.4	34.1	42.8	43.3	38.8	38.7	43.8	43.8	44.5	43.7
5	56.4	56.1	56.0	56.4	57.0	56.9	57.1	57.0	56.0	56.8
6	20.6	20.5	21.9	22.4	20.6	20.5	22.2	22.4	22.0	21.5
7	41.8	40.8	40.0	40.6	41.8	41.6	40.7	41.1	41.9	40.6
8	44.6	44.4	43.9	44.4	44.3	44.2	44.5	45.4	44.0	43.4
9	57.3	57.1	55.7	56.2	56.4	56.2	56.3	55.1	55.4	56.0
10	40.0	39.9	39.1	39.6	39.4	39.2	39.8	39.6	39.1	39.4
11	18.8	18.2	17.8	18.3	18.4	18.2	19.2	19.1	18.8	18.9
12	17.6	27.3	27.1	27.7	33.3	33.2	27.7	31.1	25.8	26.5
13	40.5	39.7	38.7	39.3	44.1	44.0	39.8	41.1	40.2	40.5
14	42.0	41.8	41.6	42.1	39.8	39.7	42.0	38.0	36.8	37.9
15	42.2	41.5	41.2	41.7	49.2	49.1	41.9	44.6	52.8	52.3
16	45.5	45.6	44.9	45.4	156.1	155.8	45.6	45.1	80.5	79.8
17	182.1	183.7	175.5	176.0	103.1	103.0	175.4	177.9	65.3	69.7
18	33.8	33.9	28.6	29.1	27.2	27.1	183.7	183.9	28.6	28.6
19	21.8	21.6	178.7	179.2	65.7	65.6	29.1	29.0	178.7	180.0
20	17.8	17.9	15.3	15.9	18.3	18.1	15.7	15.6	15.4	15.1
17-OCH_3	-	-	-	-	-	-	51.6	51.7	-	-

Recorded in ^{a}CDCl$_3$-^{b}DMSO-d$_6$-^{c}Pyridine-d$_5$ at ^{d}150 MHz-^{e}125 MHz- ^{f}100 MHz.

4. CONCLUSION

From the *n*-hexane extract of the pulp of *A. glabra*, harvested from Long Binh Ward, Thu Duc city, Vietnam, five *ent*-kaurane diterpenes including 16□-H-*ent*-kaurane-17-oic acid (**1**), 16□-H-*ent*-kaurane-17,19-dioic acid (**2**), *ent*-kaurane-16-en-19-ol (**3**), 16□-H-*ent*-kaurane-17,18-dioic acid, 17-methyl ester, (**4**), 16□1□-dihydroxykauran-19-oic acid (**5**), were isolated. The structures of the compounds were determined based on spectroscopic analysis and validated through comparison with previously published spectral data. The study reported, for the first time, the isolation of compound **1** from the species *A. glabra*.

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