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Research article

Further report on the chemical constituents of the n-hexane extract of *Leonotis nepetaefolia* (L.) R. Br (Lamiaceae)

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ABSTRACT

Introduction: *Leonotis nepetifolia* (L.) R. Br, a species of the family Lamiaceae, has some interesting biological activities, such as antibacterial, antioxidant, and anti-inflammatory activities. This paper describes the structural elucidation of seven compounds isolated from *Leonotis nepetifolia* collected in Xuyen Moc district, Ba Ria–Vung Tau Province, in June 2018. **Methods:** Phytochemical investigations of the *n*-hexane extract of *Leonotis nepetifolia* led to the isolation of seven pure compounds. Their chemical structures were elucidated by extensive MS, 1D and 2D-NMR spectroscopic analysis and comparison with previously published data. **Results:** Seven compounds, namely, (E)-10-oxooctadeca-8-enoic acid (**1**), ergosterol peroxide (**2**), turmeronol A (**3**), methyl (E)-3-(3,4-dimethoxyphenyl)propenoate (**4**), methyl 4-hydroxybenzoate (**5**), methyl (E)-3-(4-hydroxy-3-methoxyphenyl)propenoate (**6**), and alpinumisoflavone (**7**), were identified. **Conclusions:** Although these compounds are known in other species, this is the first time they have been reported in *Leonotis nepetifolia*.

Key words: Leonotis nepetifolia, ergosterol peroxide, fatty acid, turmeronol A, isoflavone

INTRODUCTION

Leonotis nepetifolia (L.) R. Br (family Lamiaceae) is native to tropical Africa and southern India. In traditional medicine, *L. nepetifolia* is used to treat bronchial asthma, diarrhea, fever, rheumatism, and malaria as an analgesic in menstrual cramps[1]. Previous studies of this plant reported that extracts and compounds isolated from this species possessed interesting biological activities: antioxidant[2], inhibition of MCF-7 (human breast cancer cell line) and Hep-2 (human larynx epithelioma cancer cell line)[3], anti-inflammatory[4], and antibacterial[5] activities. Previous phytochemical studies of L. nepetifolia showed the presence of laballenic acid, allenic acid, labdane diterpenoids, iridoids, and coumarins[6–9].

In the search for chemical constituents of *Leonotis nepetifolia*, herein, we reported a continuation study on an *n*-hexane extract to isolate seven compounds: (*E*)-10-oxooctadeca-8-enoic acid (**1**), ergosterol peroxide (**2**), turmeronol A (**3**), methyl (*E*)-3-(3,4-dimethoxyphenyl)propenoate (**4**), methyl 4-hydroxybenzoate (**5**), methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)propenoate (**6**), and alpinumisoflavone (**7**). Their chemical structures were elucidated by extensive MS, 1D and 2D-NMR spectroscopic analysis and comparison with previously published data.

MATERIALS AND METHODS

General experimental procedures

HR–ESI–MS was recorded on an HR–ESI–MS MicrOTOF–Q mass spectrometer. The LC–MSD was recorded on an 1100 Series LC/MSD Trap SL mass spectrometer. The LC–MS/MS was recorded on a ^{TM}TSQ Quantum^{TM} Access MAX triple quadrupole mass spectrometer. Optical rotations were measured on a Krüss (Germany) polarimeter with a tube length of 0.5 decimetres.

The ^{1}H-NMR 500 (MHz), ^{13}C-NMR (125 MHz) and 2D-NMR spectra were recorded on a Bruker Avance 500^{III} spectrometer. Chemical shifts are expressed in ppm using a residual solvent signal as the internal reference ($CDCl_3$ d_H 7.26, d_C 77.1).

Thin-layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} or silica gel 60 RP–18 F_{254} (Merck), and the isolated compounds were visualized by spraying with 5% vanillin/ethanol solution followed by heating. Column chromatography (CC) was performed by gravity using glass columns of appropriate sizes with silica gel (230–400 mesh RM7484-500G, Himedia) or Sephadex® LH-20 (Sigma–Aldrich).

Plant material

The *Leonotis nepetifolia plant* was collected in Xuyen Moc district, Ba Ria–Vung Tau province, in June 2018.

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The scientific name of the plant was authenticated by M.Sc. Hoang Viet, Department of Ecology and Evolutionary Biology, Faculty of Biology, University of Science, Vietnam National University Ho Chi Minh City.

Extraction and isolation

Air-dried parts of *Leonotis nepetifolia* (46 kg) were ground and extracted with methanol by the maceration method at room temperature. After filtering the solution, the solvent was evaporated under reduced pressure to obtain a crude methanolic extract (1.7 kg). This crude was used to prepare the *n*-hexane extract using the liquid–liquid partition method. The -hexane extract (460 g) was subjected to silica gel column chromatography (CC) eluted with *n*-hexane:ethyl acetate (stepwise, 99:1, 98:2, 95:5, 90:10, 50:50, 0:100, v/v) and ethyl acetate:methanol (stepwise, 99:1, 98:2, 95:5, 90:10, 50:50, 0:100, v/v) to afford 32 fractions (H1-H32). This paper reports the purification of three fractions, H2, H6, and H8. Fraction H2 (31.0 g) was divided into eight subfractions (H2.1-H2.8) by silica gel CC using the mobile phase *n*-hexane:ethyl acetate (9:1, 8:2, 5:5, 0:10, v/v). Subfraction H2.8 (3 g) was repeatedly separated by preparative TLC to afford **1** (18 mg). Fraction H6 (8.28 g) was first chromatographed on Sephadex LH-20 to give ten subfractions (H6.1-H6.10). Subfraction H6.10 (900 mg) was subjected to silica gel CC eluted by *n*-hexane:acetone (9:1) to afford **2** (5 mg). Fraction H8 (8.0 g) was subjected to silica gel CC and eluted by *n*-hexane:acetone (9:1, 8:2, 5:5, 0:10) to give five fractions: H8.1 (93 mg), H8.2 (193 mg), H8.3 (1 g), H8.4 (698 mg), and H8.5 (2.7 g). Subfraction H8.4 (698 mg) was rechromatographed by silica gel CC and eluted with *n*-hexane:chloroform (8:2) to afford two compounds **3** (7 mg) and **4** (13 mg). The same procedure was applied to fraction H8.5 (2.7 mg) eluted by *n*-hexane:acetone (stepwise, 99:1, 98:2, 95:5) to obtain **5** (10 mg), **6** (4 mg) and **7** (20 mg), respectively.

RESULTS

The chemical investigation of the -hexane extract of Leonotis *nepetifolia* (L) R. Br led to the isolation of seven compounds whose physical properties are presented in the following. The ^{1}H and ^{13}C-NMR data of compounds **1**, **2**, and **7** are presented in **Tables 1** and **3 ,** and compounds **3**– **6** are reported in **Tables 2** and **3**.

- (*E*)-10-Oxooctadeca-8-enoic acid (**1**): White wax. ESI-MS/MS (negative mode) *m/z* 295.1 $[M-H]^-$ (calcd. for $C_{18}H_{32}O_3$-H, 295.2).
- Ergosterol peroxide (**2**): White needles, mp 179–181 °C. LC–MSD (positive mode) *m/z* 429.0 $[M+H]^+$ (calcd. for $C_{28}H_{44}O_3$+H, 429.3).
- Turmeronol A (**3**): Colorless oil. HR-ESI-MS (negative mode) *m/z* 231.1386 $[M-H]^-$ (calcd. for $C_{15}H_{20}O_2$-H, 231.1385). +248 (*c* 0.43, acetone).
- Methyl (*E*)-3-(3,4-dimethoxyphenyl)propenoate (**4**): Colorless needles, mp. 69–70 °C. HR-ESI-MS (positive mode) *m/z* 223.0963 $[M+H]^+$ (calcd. for $C_{12}H_{14}O_4$+H, 223.0970).
- Methyl 4-hydroxybenzoate (**5**): White crystalline solid, mp. 112–115 °C. HR-ESI-MS (negative mode) *m/z* 151.0397 $[M-H]^-$ (calcd. for $C_8H_8O_3$-H, 151.0395).
- Methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)propenoate (**6**): Colorless needles, mp. 64–65 °C. HR-ESI-MS (positive mode) *m/z* 207.0663 $[M-H]^-$ (calcd. for $C_{11}H_{12}O_4$-H = 207.0657).
- Alpinumisoflavone (**7**): Pale yellow needles, mp. 210–213°C. HR-ESI-MS (negative mode) *m/z* 335.0914 $[M-H]^-$ (calcd. for $C_{20}H_{16}O_5$-H, 335.0919).

DISCUSSION

Compound **1** was obtained as white wax. The ^{1}H-NMR spectrum of **1** displayed signals of two olefinic protons at δ_H 6.82 (1H, *dt*, 16.0, 6.5 Hz, H-8) and 6.08 (1H, *d*, 15.5 Hz, H-9). The large coupling constants of 16.0 Hz of protons H-8 and H-9 suggested the *E*-configuration of this double bond. The proton spectrum also showed a terminal methyl group [δ_H 0.87 (3H, *t*, 7.0 Hz, H-18)] and two methylene groups next to two carbonyl groups [δ_H 2.51 (2H, *t*, 7.0 Hz, H-11) and 2.44 (2H, *t*, 7.0 Hz, H-2)]. The ^{13}C-NMR spectrum (Table 3) showed two olefinic carbons [δ_C 146.9 (C-8), 130.5 (C-9)], one terminal methyl carbon [δ_C 14.2 (C-18)] and some methylene groups at δ_C 22–41. The spectrum did not reveal the two quaternary carbonyl carbons C-1 and C-10.

The ESI-MS/MS spectrum of **1** (Figure 3) showed a pseudomolecular ion peak at *m/z* 295.1 $[M-H]^-$. The MS/MS (negative mode) fragment patterns (Figure 3) suggested that **1** possessed a double bond at C-8, and this bond was adjacent to a ketone (C-10). These positions were supported by the HMBC experiment (Figure 2) with cross-peaks of protons H-8, H-9, H-11 to the carbon signal at δ_C 200.1 (conjugated ketone

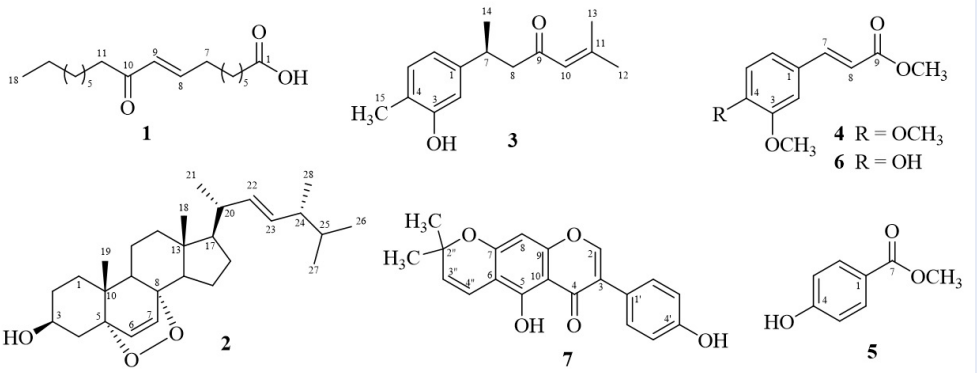

Figure 1: Chemical structures of seven isolated compounds

carbon, C-10) and of protons H-2 to the carbon signal at δ_C 169.7 (carboxyl carbon, C-1). The comparison of NMR and MS data of **1** with those of (*E*)-10-oxooctadeca-8-enoic acid[10], a synthetic compound obtained from the oxidation of oleic acid, showed good compatibility. Therefore, the chemical structure of **1** was suggested to be (*E*)-10-oxooctadeca-8-enoic acid.

Compound **2** was isolated as white needles. The LC–MSD-MS spectrum showed a pseudomolecular ion peak at *m/z* 429.0 $[M+H]^+$ (calcd. for $C_{28}H_{44}O_3$+H, 429.3). The ^{1}H-NMR spectrum of **2** showed signals of six methyl groups [δ_H 1.00 (3H, *d*, 7.0 Hz, H-21), 0.91 (3H, *d*, 6.5 Hz, H-28), 0.83 (3H, *d*, 7.0 Hz, H-27), 0.82 (3H, *d*, 7.0 Hz, H-26), 0.82 (3H, *s*, H-18) and 0.88 (3H, *s*, H-19)], one oxygenated methine [δ_H 3.97 (1H, *m*, H-3)], two double bonds [δ_H 5.15 (1H, *dd*, 15.5, 7.0 Hz, H-22),

5.22 (1H, *dd*, 15.0, 7.5 Hz, H-23), 6.24 (1H, *d*, 8.5 Hz, H-6) and 6.50 (1H, *d*, 8.5 Hz, H-7)]. Its corresponding ^{13}C-NMR spectrum showed 28 signals with four olefinic carbons [δ_C 130.9 (C-7), 132.5 (C-23), 135.6 (C-6) and 135.4 (C-22)] and two oxygenated quaternary carbons [δ_C 82.3 (C-5) and 79.6 (C-8)] of an ergosterol peroxide derivative. The good compatibility of its NMR and MS data with those of ergosterol peroxide in the literature[11] suggested that compound **2** was ergosterol peroxide.

Compound **3** was isolated as a colorless oil. Its molecular formula was determined as $C_{15}H_{20}O_2$ through its pseudomolecular ion peak at *m/z* 231.1386 $[M-H]^-$ (calcd. for $C_{15}H_{20}O_2$-H, 231.1385). The ^{1}H-NMR spectrum (Table 2) showed four methyl groups [δ_H 2.20 (3H, *s*, H-15), 2.11 (3H, *s*, H-13), 1.86 (3H, *s*, H-12), 1.23 (3H, *d*, 7.0 Hz, H-14)], one olefinic proton [δ_H 6.02 (1H, *s*, H-10)], a set of 1,3,4-trisubstituted benzene ring signals [δ_H 7.02 (1H, *d*, 7.5 Hz, H-5), 6.70 (1H, *dd*, 7.5, 1.5 Hz, H-6) and 6.66 (1H, *d*, 1.5 Hz, H-2)], a methine adjacent to a methylene [δ_H 3.24 (1H, *sextet*, 7.0 Hz, H-7), 2.70 (1H, *dd*, 15.5, 6.0 Hz, H-8a), 2.59 (1H, *dd*, 15.5, 6.0 Hz, H-8b)]. The ^{13}C-NMR spectrum of **3** showed six aromatic carbons [δ_C 155.4 (C-3), 146.2 (C-1), 131.1 (C-5), 121.5 (C-4), 119.1 (C-6), 113.7 (C-2)], two olefinic carbons at δ_C 154.0 (C-11), 124.3 (C-10), four methyl groups [δ_C 27.8 (C-12), 22.1 (C-14), 20.9 (C-13), 15.5 (C-15)], and one carbonyl group at δ_C 200.1 (C-9). Due to the compatibility of the specific optical rotation {Compound **3:** +248 (*c* 0.43, acetone) and turmeronol A: +63 (*c* 0.1, chloroform)[12]} and NMR data with corresponding data in the literature[13], **3** was turmeronol A.

Compound **4** was obtained as colorless needles. Compound **4** possessed a 1,3,4-trisubstituted benzene ring with proton NMR signals at δ_H 7.10 (1H, *dd*, 8.0, 2.0 Hz, H-6), 7.04 (1H, *d*, 1.5 Hz, H-2), 6.86 (1H, *d*, 8.5 Hz, H-5). The ^{1}H-NMR spectrum also showed a six-proton singlet at δ_H 3.90 (6H, *s*) for the two methoxy groups and two olefinic protons at δ_H 7.63 (1H, *d*, 16.0 Hz, H-7), 6.30 (1H, *d*, 16.0 Hz, H-8) of an *E*-configuration double bond. The ^{13}C-NMR spectrum of **4** showed signals of one carboxyl carbon (δ_C 167.8, C-9), two olefinic carbons (δ_C 144.9, C-7 and 115.7, C-8), six aromatic carbons [δ_C 151.4 (C-4), 149.5 (C-3), 127.6 (C-1), 122.7 (C-6), 111.3 (C-5), 110.0 (C-2)] and three methoxy groups [δ_C 56.1 (3-OCH_3 and 4-OCH_3) and 51.7 (9-OCH_3)]. In addition, the HR-ESI-MS spectrum of compound **4** showed a pseudomolecular ion peak at *m/z* 223.0963 $[M+H]^+$ (calcd. for $C_{12}H_{14}O_4$+H, 223.0970).

The comparison of these HR-MS and NMR data of **4** with those of methyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate in the literature[14]

Table 1: The ^{1}H-NMR ($CDCl_3$, 500 MHz) data of compound 1, 2, 7

N^o	1	2	N^o	7
2	2.44 (*t*, 7.0)		2	7.81 (*s*)
3		3.97 (*m*)	3	
6		6.24 (*d*, 8.5)	6	
7	2.19 (*m*)	6.50 (*d*, 8.5)	7	
8	6.82 (*dt*, 16.0, 6.5)		8	6.34 (*s*)
9	6.08 (*d*, 15.5)	1.50 (*m*)	9	
11	2.51 (*t*, 7.0)		1’	
12			2’, 6’	7.34 (*d*, 8.5)
13			3’, 5’	6.83 (*d*, 8.5)
15			3”	5.62 (*d*, 10.0)
16			4”	6.73 (*d*, 10.5)
18	0.87 (*t*, 7.0)	0.82 (*s*)	2”-CH_3	1.48 (6H, *s*)
19		0.88 (*s*)	5-OH	13.08 (*s*)
20				
21		1.00 (*d*, 7.0)		
22		5.15 (*dd*, 15.5, 7.0)		
23		5.22 (*dd*, 15.0, 7.5)		
25		1.47 (*m*)		
26		0.82 (*d*, 7.0)		
27		0.83 (*d*, 7.0)		
28		0.91 (*d*, 6.5)		

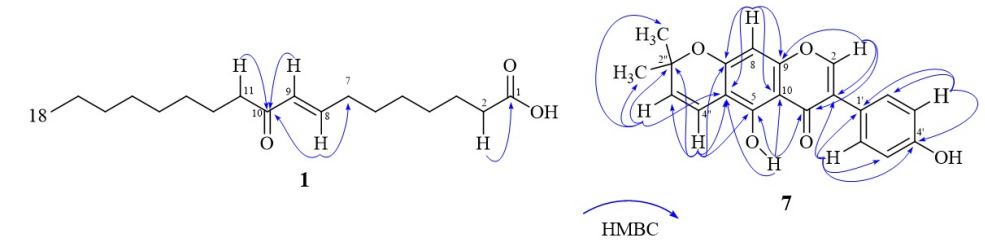

Figure 2: Keys HMBC of compounds **1** and **7**

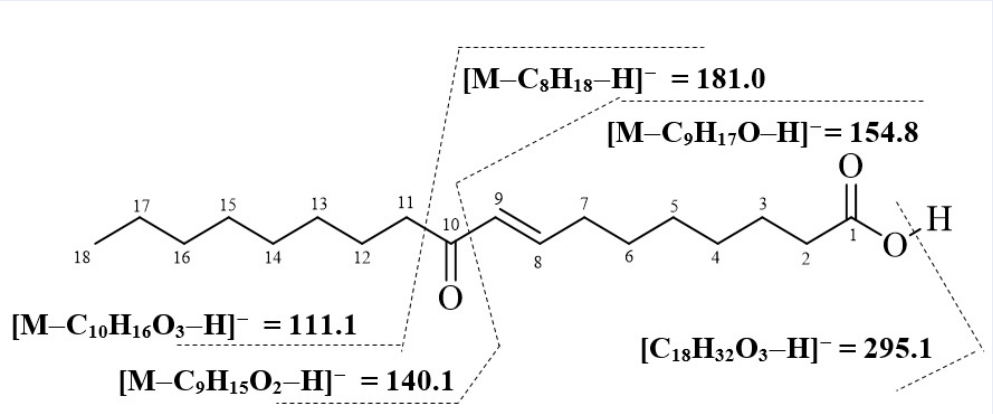

Figure 3: The (negative mode) MS/MS fragment patterns of compound **1**

Table 2: The ^{1}H-NMR ($CDCl_3$, 500 MHz) data of compound 3– 6

N^o	3	4	5	6
2	6.66 (*d*, 1.5)	7.04 (*d*, 1.5)	7.95 (*d*, 8.5)	7.02 (*d*, 1.5)
3			6.88 (*d*, 9.0)	
5	7.02 (*d*, 7.5)	6.86 (*d*, 8.5)	6.88 (*d*, 9.0)	6.92 (*d*, 8.0)
6	6.70 (*dd*, 7.5, 1.5)	7.10 (*dd*, 8.0, 2.0)	7.95 (*d*, 8.5)	7.07 (*dd*, 8.0, 2.0)
7	3.24 (*sextet*, 7.0)	7.63 (*d*, 16.0)		7.62 (*d*, 16.0)
8	2.70 (*dd*, 15.5, 6.0) 2.59 (*dd*, 15.5, 8.0)	6.30 (*d*, 16.0)		6.29 (*d*, 15.5)
10	6.02 (*s*)			
12	1.86 (*s*)			
13	2.11 (*s*)			
14	1.23 (*d*, 7.0)			
15	2.20 (*s*)			
3-OCH_3		3.90 (*s*)		3.92 (*s*)
4-OCH_3		3.90 (*s*)		
9-OCH_3		3.80 (*s*)		3.79 (*s*)
7-OCH_3			3.90 (*s*)	
4-OH			6.20 (*brs*)	5.89 (*brs*)

showed good *compatibility. Therefore,* ***4*** *was* methyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate with the systematic name methyl (*E*)-3-(3,4-dimethoxyphenyl)propenoate.

Compound **6** was obtained as colorless needles. The molecular formula was determined to be $C_{11}H_{12}O_3$ through its pseudomolecular ion peak at *m/z* 193.0501 $[M+H]^+$ (calcd. for $C_{11}H_{12}O_3$+H, 193.0864). The similarity in the NMR data (**Tables 2 and 3**) of **6** and **4** with just one difference of the replacement of the methoxy group of the benzene ring in **4** [δ_H 3.90 (3H, *s*, 4-OCH_3)] by a hydroxy group in **6** [δ_H 5.89 (1H, *brs*, 4-OH)] suggested that the latter was methyl ferulate[15] or its systematic name,methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)propenoate.

Compound **5** was isolated as a white crystalline solid. Its MS spectrum showed a deprotonated molecular ion peak at *m/z* 151.0397 $[M-H]^-$ (calcd. for

Table 3: ^{13}C-NMR ($CDCl_3$, 125 MHz) data of compound 1– 7

N^o	1	2	3	4	5	6	N^o	7
1	169.7	34.9	146.2	127.6	122.7	127.2	2	152.8
2	35.3	30.3	113.7	110.0	132.1	109.6	3	123.8
3	24.3	66.6	155.4	149.5	115.4	148.2	4	181.2
4	28.0	37.1	121.5	151.4	160.3	147.0	5	157.0
5	29.5	82.3	131.1	111.3	115.4	115.4	6	105.8
6	29.6	135.6	119.1	122.7	132.1	123.2	7	159.8
7	32.60	130.9	35.5	144.9	167.4	145.1	8	95.1
8	146.9	79.6	52.8	115.7		114.9	9	157.5
9	130.5	51.3	200.1	167.8		167.8	10	106.3
3-OCH_3				56.1		56.1	1’	123.0
4-OCH_3				56.1			2’	130.5
9-OCH_3				51.7		51.7	3’	115.9
7-OCH_3					52.1		4’	156.2
10	200.1	37.1	124.3				5’	115.9
11	40.3	23.6	154.0				6’	130.5
12	24.5	39.5	27.8				2”	78.3
13	28.3	44.7	20.9				3”	128.4
14	29.3	51.9	22.1				4”	115.6
15	29.2	20.8	15.5				2”-CH_3	28.5
16	32.0	28.8						
17	22.8	56.4						
18	14.2	13.0						
19		18.3						
20		39.9						
21		21.0						
22		135.4						
23		132.5						
24		42.9						
25		33.2						
26		19.8						
27		20.1						
28		17.7						

$C_8H_8O_3$-H, 151.0395). The ^{1}H-NMR spectrum (Table 2) showed four aromatic proton signals [δ_H 7.95 (2H, *d*, 8.5 Hz, H-2, H-6) and 6.88 (2H, *d*, 9.0 Hz, H-3, H-5)] of a 1,4-disubstituted benzene ring, a phenolic hydroxyl [δ_H 6.20 (1H, brs, 4-OH)] and one methoxy group [δ_H 3.90 (3H, *s*, COOC**H**$_3$)]. The ^{13}C-NMR spectrum (Table 3) showed six aromatic signals for one carboxyl carbon [δ_C 167.4 (C-7)] and one methoxy group [δ_C 52.1 (**C**OOCH$_3$)]. Thus, **5** was assigned as methyl 4-hydroxybenzoate[16].

Compound **7** was obtained as pale yellow needles. Its ^{1}H-NMR spectrum showed proton signals at δ_H 13.08 (1H, *brs*, 5-OH), 7.81 (1H, *s*, H-2), 7.34 (2H, *d*, 8.5 Hz, H-2', H-6'), 6.83 (2H, *d*, 8.5 Hz, H-3', H-5'), 6.73 (1H, *d*, 10.5 Hz, H-4"), 6.34 (1H, *s*, H-8), 5.62 (1H, *d*, 10.0 Hz, H-3") and 1.48 (6H, *s*, two methyl groups, 2"-CH$_3$). The proton NMR data of **7** were almost identical to those of 4'-*O*-methylalpinumisoflavone, a compound previously isolated from a less polar H5 fraction, with one difference of lacking the methoxy signal at δ_H 3.84 in the former[17]. The comparison of the ^{13}C-NMR data of these two compounds as well as that of alpumisoflavone[18] showed good compatibility. This was further supported by the HR-ESI-MS spectrum with a deprotonated molecular ion peak at *m/z* 335.0914 [M-H]$^-$ (calcd. for $C_{20}H_{16}O_5$-H, 335.0919) and by all appropriate cross-peaks in the HMBC spectrum (Figure 2). Therefore, the chemical structure of **7** was proposed as alpumisoflavone.

CONCLUSION

Further chemical studies on the *n*-hexane extract of Leonotis nepetifolia (L.) R. Br, collected at Xuyen Moc district, Ba Ria–Vung Tau province, using some column chromatographic separations, seven compounds were isolated. Their structures were elucidated as *(E)*-10-oxooctadeca-8-enoic acid (**1**), ergosterol peroxide (**2**), turmeronol A (**3**), methyl (*E*)-3-(3,4-dimethoxyphenyl)propenoate (**4**), methyl 4-hydroxybenzoate (**5**), methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)propenoate (**6**), and alpinumisoflavone (**7**). Although these compounds are known in other species, this is the first time they have been reported in *L. nepetifolia*.

ABREVIATIONS

LC–MSD: Liquid chromatograph/mass selective detector

LC–MS/MS: Liquid chromatography with tandem mass spectrometry

HR-ESI-MS: High resolution electrospray ionization-mass spectrometry

^{1}H NMR: Proton Nuclear Magnetic Resonance

^{13}C NMR: Carbon-13 Nuclear Magnetic Resonance

HMBC: Heteronuclear Multiple Bond Correlation

s: singlet

d: doublet

dd: doublet of doublets

t: triplet

m: multiplet

COMPETING INTEREST

The authors declare no competing financial interest.

AUTHORS' CONTRIBUTION

Nguyen T.K.H., Phan T.T., Le N.H.T. interpreted NMR and MS data and searched the bibliography. Nguyen K.P.P., Ngo T.T.D. contributed to conducting experiments and acquiring MS and NMR data and gave the final correction for the manuscript.

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