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Chemical constituents from *Piper betle* L. Var Nigra (Piperaceae)

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Abstract

Two fatty acid derivatives, 2-octenoic acid and 2-hexenoic acid were isolated from the extract of *n*-hexane of the *Piper betle* L. Var. Nigra (Piperaceae). The chemical structures were identified on the basis of spectroscopic evidence and compared to previously reported spectra. These isolated compounds appear for the first time in the plant.

Keywords: *Piper betle* L. Var. Nigra, fatty acid, 2-octenoic acid and 2-hexenoic acid

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1. Introduction

Piper betle L., belonging to Piperaceae family, known as a traditional herbal medicinal plant and used for several health benefits in Asian countries. Currently, demand for its products such as herbal drugs, medicines, and natural herbal formulations has increased. The beneficial effects of betel leaves and its products have traditionally exploited for the treatment of several diseases like bad breath, cuts, injuries, inflammations, cold cough, indigestion, etc. Betel leaf has several characteristics such as nutritional, organoleptic, therapeutic, prophylactic, functional, antimicrobial, antioxidant and other desirable qualities which can provide a challenging opportunity to the food scientists and technologists to develop novel food products with enhanced food safety, extended shelf life. The leaf extract and EO having the above-discussed properties can also be explored for manufacturing a large number of cosmetics, medicines, pharmaceuticals, food product development in the food sector [1].

Piper betle L. var. *nigra* or black betle (in Indonesia known as Sirih Hitam) is a tropical

plant closely related to the common piper and belongs to the Piperaceae family and the genus of piper. This genus consists of five subgenera and approximately 1400 species spread throughout tropical and subtropical regions and widely cultivated in Indonesia, India, Sri Lanka, Malaysia, Thailand, Taiwan, and other Southeast Asian countries and has a long history of over 2000 years.

Till now, a broad range of bioactive compounds including polyphenols, terpenes, etc., has been identified from the extracts and essential oil (EO) of betel leaves. The structural and functional characterization of the extract and EO bio-actives has been derived by various advanced standard methods. Most of the health-related benefits of betel leaves have been associated with their bioactive phenolic compounds. The extract of this highly perishable product can be used in organic synthesis, food, and beverage industry, pharmaceuticals, etc., to the environmental issues. The present review provides information on extraction techniques, identification of bioactive compounds, and their biological activities. That apart, information on processing, preservation, and health benefits along with their mechanisms has also been added [1].

In a previous study of Piper betle L. Var. nigra Two amide derivatives, piperenamide A-B have also been reported to have activity against two oral pathogenic bacteria and opportunistic pathogenic [2].

Various active compounds are present in *Piper betle* such as allylpyrocatechol, hydroxychavicol, piperbetol, ethylpiperbetol, piperol A, piperol B, chavibetol, and alkaloids which account for these beneficial medicinal properties [3]. According to Burfield a typical EO from *Piper betle* leaves is dominated by phenylpropanoids and aromatic compounds, can contain up to 40% eugenol, and up to 40% of carvacrol and chavicol taken together, while chavibetol is characteristic of the EOs from the whole plant. Other typical compounds are α terpinene, *p*-cymene, 1,8-cineole, β-caryophyllene, α-humulene, allyl pyrocatechol, allylcatechol, methyl eugenol, and estragol (methyl chavicol) [4].

During the efforts to discover more structurally distinct natural products from this species, we encountered a new compound (Fig 1) isolated from *Piper betle* var. *nigra* leaves. Their chemical structures were elucidated by detailed spectroscopic data analysis. Herein, we present the isolation and structural elucidation of these compounds.

2. Experimental section

2.1. General

UV spectra was measured using a TECAN Infinite M200 pro, with MeOH. The IR spectra and mass spectra were recorded on a SHIMADZU IR Prestige-21 in KBr and Waters Xevo QTOF MS respectively. Using a JEOL ECZ-500, the NMR data was recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C, using TMS as internal standard. Column chromatography was conducted on the silica gel 60 (<70, 70–230 and 230–400 mesh, Merck), after which TLC analysis was carried out on 60 GF_{254} (Merck, 0.25 mm) using various solvent systems, in order to detect spots by irradiating under ultraviolet-visible light (257 and 364 nm) and heating of silica gel plates, sprayed with H_2SO_4 in N-hexane (10%).

2.2. Plant Material.

The leaf of *P. betle L. var Nigra* were collected from Furthermore, the plant was identified by Mr. Ismail, a staff of the Bogoriense Herbarium, Bogor, Indonesia. Finally, a voucher specimen (No. Bo-104) was deposited at the Herbarium.

2.3. Extraction and isolation.

The dried ground leaf (473.21 g) of *P. betle L. var Nigra* was extracted with ethanol 70% (14 L), at room temperature for 7 days. After removal of the solvent under vacuum, the viscous concentrate *n*-hexane extract (9.11 g) was obtained. The *n*-hexane extract (9.11 g) was fractionated by column chromatography on silica gel, using a gradient of *n*-hexane, EtOAc and MeOH (10% stepwise) resulting into eight fractions (A–H). Fraction A (1.12 g) was subjected to column chromatography on silica gel using *n*-hexane-$CHCl_3$ (5% stepwise), as eluting solvents to afford seven subfractions (A1-A7). Subfraction A3 (632.2 mg) was chromatographed on a column of silica gel, eluted with *n*-hexane: CH_2Cl_3 (7:3), to give six

subfractions (A3A–A3G). Similarly, subfraction A3D (100.1 mg) was chromatographed on silica gel eluted with *n*-hexane: CH_2Cl_3: EtOAc (7:2.5:0.5), to give **1** (6.1 mg). Subfraction A3E (90.2 mg) was chromatographed on silica gel eluted with petroleum ether: $CHCl_3$ (7:2), to give **2** (4.8 mg).

2.3.1 2-octenoic acid (1)

Oil yellow; HR-TOFMS *m/z* 143.1019 [M-H]$^+$ (cal. $C_8H_{15}O_2$ *m/z* 143.1094), ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.92 (3H, t, *J* = 6.8 Hz, H_3-8), 1.26-1.33 (6H, m, H_2-5 – H_2-7), 2.20 (2H, m, H_2-4), 5.35 (1H, dd, *J* = 15.2 and 5.6 Hz, H-3), 5.77 (1H, d, *J* = 15.2 Hz, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 14.0 (C-8), 22.6 (C-7), 26.8 (C-6), 29.6 (C-5), 31.9 (C-4), 121.6 (C-2), 129.8 (C-3), 168.8 (C-1).

2.3.2 2-hexenoic acid (2)

Oil yellow; HR-TOFMS *m/z* 115.1211 [M-H]$^+$ (cal. $C_6H_{11}O_2$ *m/z* 115.1094), ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.92 (3H, t, *J* = 6.8 Hz, H-6), 1.33 (2H, m, H-5), 1.03 (2H, m, H-4), 5.35 (1H, *J* = 15.0 and 5.6 Hz, H-3), 5.77 (1H, d, *J* = 15.0 Hz, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 14.4 (C-6), 22.6 (C-5), 26.8 (C-4),122.6 (C-2), 130.1 (C-3), 167.6 (C-1).

3. Results and Discussion

The *n*-hexane extract from the leaf of *P. betle* L. var Nigra was fractionated by column chromatography on silica gel, using a gradient of *n*-hexane, EtOAc and MeOH (10% stepwise). The fractions were repeatedly subjected to normal phase column chromatography, to accommodate compounds **1-2**.

2-octenoic acid (**1**) was observed as an Oil yellow, with its molecular composition established as $C_8H_{14}O_2$, based on HR-TOFMS. This showed a [M+H]+ ion peak at *m/z* 143.1019 (calcd. $C_8H_{15}O_2$ *m/z* 143.1094), requiring two degrees of unsaturation. The ^{1}H-NMR spectrum (Table 1) showed one primary methyl at δ_H 0.92 (3H, t, 6.8 Hz, H_3-8), two sp^2 methine protons at δ_H 5.77 (1H, d, *J*= 15.2 Hz, H-2), 5.35 (1H, dt, *J*= 5.6; 15.2 Hz, H-3) indicates trans double bonds and four methylenes at δ_H 1.26-1.33 (6H, m, H_2-5–H_2-7), 2.03 (2H, m, H_2-4). The ^{13}C NMR together with the DEPT spectra revealed eight carbons consisting of a carbonyl at δ_C 168.8 (C-1), α,β,-unsaturated secondary at δ_C 121.6 (C-2) and 129.8 (C-3), four carbons methylene at δ_C 22.6 (C-7), 26.8 (C-6), 29.6 (C-5), 31.9 (C-4) and one methyl at δc 14.0 (C-8).

The ^{1}H-^{1}H COSY spectrum of compound **1** showed correlations in H2-H3-H4-H5-H6-H7 and H8, supporting the presence of a secondary fatty acid [3]. The HMBC correlations from H-2 to C-1 and C-4; H-3 to C-1, C-2 and C-5; H-4 to C-1, C-2 and C-6, H-5 to C-3 and C-7; H-6 to C-8; H-7 to C-5 and C-8, H-8 to C-6 and C-7, which was verified by correlations observed in the ^{1}H-^{1}H COSY and HMBC spectra (Figure 2).

2-hexenoic acid (**2**) was observed as an Oil yellow, with its molecular composition established as $C_6H_{10}O_2$, based on HR-TOFMS. This showed a [M+H]+ ion peak at *m/z* 115.1211 (calcd. $C6H_{11}O_2$ *m/z* 115.1094), requiring two degrees of unsaturation. The ^{1}H-NMR spectrum (Table 1) showed one primary methyl at δ_H 0.92 (3H, t, 6.8 Hz, H_3-6), two sp^2 methine protons at δ_H 5.77 (1H, d, *J*= 15.0 Hz, H-2), 5.35 (1H, dt, *J*= 5.6; 15.0 Hz, H-3) indicates trans double bonds and two methylenes at δ_H 2.03 (2H, m, H_2-4), 1.33 (2H, m, H_2-5). The ^{13}C NMR together with the DEPT spectra revealed six carbons consisting of a carbonyl at δ_C 167.6 (C-1), α,β,-unsaturated secondary at δ_C 122.6 (C-2) and 130.1 (C-3), two carbons methylene at δ_C 22.6 (C-5), 26.8 (C-4) and one methyl at δc 14.0 (C-8)

The ^{1}H-^{1}H COSY spectrum of compound **2** showed correlations in H2-H3-H4-H5 and H6, supporting the presence of a secondary fatty acid [3]. The HMBC correlations from H-2 to C-1 and C-4; H-3 to C-1, C-2 and C-5; H-4 to C-1, C-2 and C-6, H-5 to C-3 and C-5; H-6 to C-5 and C-4, which was verified by correlations observed in the ^{1}H-^{1}H COSY and HMBC spectra (Figure 2).

Tabel 1. NMR data compound **1-2** (500 MHz for ^{1}H dan 125 MHz for ^{13}C)

Position Carbon	1		2	
	^{13}C-NMR δ_C (mult.)	^{1}H-NMR δ_H [(ΣH, mult, *J*(Hz)]	^{13}C-NMR δ_C (ppm)	^{1}H-NMR δ_H [(ΣH, mult, *J*(Hz)]
1	168.8	-	167.6	-
2	121.6	5.77 (1H, d, 15.2)	122.6	5.77 (1H, d, 15.0)
3	129.8	5.35 (1H, dt, 15.2; 5.6)	130.1	5.35 (1H, dt, 15.0; 5.6)
4	31.9	2.03 (2H, m)	26.8	2.03 (2H, m)
5	29.6	1.26-1.33 (2H, m)	22.6	1.33 (2H, m)
6	26.8	1.26-1.33 (2H, m)	14.4	0.92 (3H, t, 6.8)
7	22.6	1.26-1.33 (2H, m)	-	-
8	14.0	0.92 (3H, t, 6.8)	-	-

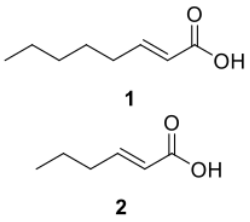

Figure 1. Structure of Compounds (**1-2**)

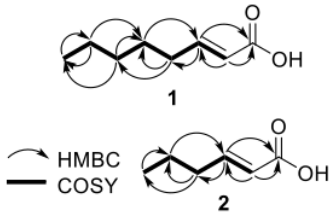

Figure 2. Selected HMBC and COSY correlations for Compounds (**1-2**)

4. Conclusion

The report of two fatty acid derivatives, 2-octenoic acid (**1**) and 2-hexenoic acid (2) in *P. betle* L. Var. nigra.

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Conflict of Interest

The authors declare there is no conflict of interest.

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