Short Communication:

Arohynapene A Produced by *Penicillium steckii* JB-NW-2-1 Isolated from *Avicennia marina* (Forssk.) Vierh and Its Cytotoxic Activities

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Abstract: *Mangrove-associated endophytic fungi are producers of secondary metabolites in unique and diverse structures with interesting biological activities such as antiviral, antifungal, antibacterial, anti-inflammatory, and cytotoxic agents. Endophytes play an important role in the physiological activities of the host plants, influencing the improvement of resistance to stress, insects, nematodes, and diseases. In this study, arohynapene A, a polyketide compound, was successfully isolated from the mangrove-derived fungus* Penicillium steckii *JB-NW-2-1 obtained from mangrove plant* Avicennia marina *(Forssk) Vierh. The structure was determined by a spectroscopic method including IR, MS, 1D-, and 2D-NMR techniques. This compound was evaluated for cytotoxic activities using resazurin assay against four cancer cells, HeLa cervical, MCF-7 breast cancer, B16-F10 melanoma, and A549 lung adenocarcinoma. The results showed no significant activities against all cancer cells tested (IC_{50} > 500 μM).*

Keywords: *Arohynapene A;* Avicennia marina*; cytotoxic; endophytic fungi; polyketide*

■ INTRODUCTION

Salt-tolerant forest ecosystems are found in the intertidal zones of sheltered beaches, estuaries, tidal creeks, backwaters, lagoons, marshes, and mudflats in tropical and subtropical latitudes known as mangroves. Mangrove forests are biodiversity hotspots for marine fungi [1-2]. In mangrove ecosystems, many endophytes, including fungal endophytes, play an important role in facilitating mangrove adaptation. These endophytes have gained significant attention as potential sources of novel secondary metabolites, utilizing the rich diversity of the marine environment to produce unique compounds. The ability of endophytes to produce structurally distinct phytocompounds with important biomedical and biopharmaceutical implications has intrigued many researchers [3-6]. Since mangrove plants produce secondary metabolites that are chemically unique and diverse, mangrove-derived endophytes are expected to produce a variety of structurally unique and pharmacologically active metabolites. Chemical investigation of mangrove endophytes has revealed the

existence of several bioactive secondary metabolites with a variety of structural features, including alkaloids, terpenoids, chromones, coumarins, polyketides, and peptides [7-8].

Penicillium is a cosmopolitan genus of molds comprising over 350 species that play various roles in natural ecosystems, agriculture, and biotechnology [9]. *Penicillium* has become one of the best-known fungal genera for bioactive compound discovery [10-11]. Over time, the exploration of *Penicillium* species, especially endophytes, has broadened well beyond their capacity to generate antibiotic compounds and a diverse array of biological activities. This genus has produced anthraquinones, benzodiazepines, coumarins, diketopiperazines, ergot alkaloids, polyketides, quinolines, quinazolines, steroids, and terpenoids [12-13]. Several bioactive compounds from *Penicillium* exhibit a range of biological activities, including antimicrobial, anticancer, antiviral, antioxidant, anti-inflammatory, antiparasitic, immunosuppressant, antidiabetic, anti-obesity, antifibrotic, neuroprotective, and insecticidal effects. [14]. Marine-derived *Penicillium* fungi are becoming a promising reservoir of marine natural products with bioactivities and novel structures [15].

In this study, we investigated the endophytic fungus *Penicillium steckii* derived from the mangrove plant *Avicennia marina* (Forssk) Vierh. *A. marina* is one of the mangroves that have a pharmacological potential. *A. marina* (Forssk.) Vierh. is a well-known plant with a rich history of use in traditional and folk medicine. This evergreen tree belongs to the Acanthaceae family. The plant's pharmacological activity is attributed to the presence of several phytochemical classes, including flavonoids, terpenoids, glycosides, and steroids [16]. The secondary metabolites produced by the endophytic fungi derived from *A. marina* has also unique structures and are pharmacologically active [17]. Six new disulfide-bridged diketopiperazine derivatives, brocazines A–F were isolated from *Penicillium brocae* MA-231, a fungus obtained from the fresh tissue of *A. marina* [18]. Chen et al. [19] have successfully isolated four new polyketide compounds: penicillol A, penicillol B, citreoviridin H, and citreoviridin I. In our continuous studies of phytochemical investigations from mangrove-derived fungi, we isolated arohynapene A, a polyketide compound, using potato dextrose broth as a medium for the fermentation process. This study also provides isolation, structural elucidation, and cytotoxic activity against HeLa cervical, MCF 7 breast cancer, B16-F10 melanoma, and A549 lung adenocarcinoma cancer cells.

■ EXPERIMENTAL SECTION

Materials

The solvent used includes *n*-hexane, ethyl acetate, methanol (technical grade) followed by distillation, and chloroform (99% purity Merck, Germany). Column chromatography was conducted on silica gel 60 (Merck, Germany). TLC was performed on Merck 60 F_{254} silica gel plates.

Instrumentation

The melting point was measured with a Fisher-John melting point apparatus. Optical rotation was measured using an ATAGO AP-300 automatic polarimeter (Saitama, Japan). IR spectra were recorded in a KBr plate using a Perkin Elmer Spectrum 100 FTIR spectrometer (Perkin Elmer, Shelton, USA). The mass spectra resolution was determined using a Water Xevo Q-TOF direct probe/MS system in ESI mode with a microchannel plates MCPs detector (Milford, MA, USA). NMR spectra were obtained with a JEOL JNM-ECX500R/S1 spectrometer (JEOL, Tokyo, Japan) operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C, with TMS as an internal standard. Column chromatography (CC) was performed using silica gel 60 (70–230 and 230–400 mesh, Merck, Darmstadt, Germany). Silica gel GF_{254} (0.25 mm, Merck, Darmstadt, Germany) was used to precoat the thin-layer chromatography (TLC) plates. Spot detection was achieved by spraying with a 10% H_2SO_4 solution in ethanol, followed by heating.

Procedure

Collection of fungal and plant material

The plant material was collected from Blanakan District, Subang Regency, West Java, Indonesia (6°16'52" S, 107°39'46" E). The plant was determined to

be *Avicennia marina* (Forssk.) Vierh by Mochamad Untung Kurnia Agung (Marine Science Lecturer at the Marine Science Department, Faculty of Fisheries and Marine Science, Universitas Padjadjaran). The fungi were isolated from the inner tissue of *A. marina*'s root. This endophytic fungus was identified by molecular analysis of the internal transcribed region (ITS) and is known as *P. steckii* strain JB-NW-2-1 (Gen Bank Accession number MG554368.1).

Fermentation and compound isolation

P. steckii strain JB-NW-2-1 was fermented on potato dextrose broth (PDB) media (100 mL, 60 flask) for 30 d. After 30 d, the PDB culture was filtered, and the media was extracted with ethyl acetate and evaporated in a vacuum to give an extract of 2.2 g. Ethyl acetate extract was chromatographed on silica gel CC using a stepwise gradient (10%) of *n*-hexane: EtOAc (100:0–0:100) and continued with EtOAc: MeOH (100:0–0:100) to yield 13 fractions (Fr. 1-1 to 1-13). Fr 1-7 (100 mg) was further separated on silica gel CC with stepwise gradient (5%) of $CHCl_3$/EtOAc (100:0–0:100) to provide 8 fractions (Fr. 1-7.1 to 1-7.8) and Fr.1-7.7 is compound **1** (7.5 mg).

Arohynapene A (1). White powder, m.p. 171–174 °C, $[\alpha]_D^{20}$ + 68.4 (*c* 0.1, MeOH); IR (KBr) ν_{max} (cm^{-1}) 3266 (O–H stretch), 2961 (C–H sp^3 stretch), 1638 (C=O stretch), 1599 (C=C stretch), and 1293 (C–O stretch). ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz), see Table 1; HR-TOFMS (negative ion mode) *m/z* 285.1491 $[M-H]^+$ (calcd. for $C_{18}H_{21}O_3$, *m/z* 285.1491).

Determination of cytotoxic activity

The cytotoxic effects of compound **1** were assessed using the PrestoBlue® assay and cell viability with resazurin base. The cells were cultured in Rosewell Park Memorial Institute (RPMI) medium supplemented with 10% (v/v) Fetal Bovine Serum (FBS) and 1 µL/mL antibiotic. The cells were cultured in 96-well plates at 37 °C under 5% CO_2 incubation until they reached a density of 1.7×10^4 cells/well. The medium was then replaced with fresh medium containing samples of varying

Table 1. The NMR data of **1** *^{1}H-NMR (500 MHz, CD_3OD), ^{13}C-NMR (125 MHz, CD_3OD)(left) compared with the literature, arohynapene A **^{1}H-NMR (400 MHz, $CDCl_3$), ^{13}C-NMR (100 MHz, $CDCl_3$) (right) [20]

No	^{13}C (ppm)*	HMQC δH (ΣH, mult., *J* in Hz,)*	^{13}C (ppm)**	HMQC δH (ΣH, mult., *J* in Hz)**
1	169.4 (s)		171.3 (s)	
2	120.9 (d)	5.92 (1H, d, 15.5)	112.0 (d)	5.93 (1H, d, 15.5)
3	145.1 (d)	7.48 (1H, dd, 15.5, 11.0)	146.8 (d)	7.57 (1H, dd, 15.5, 11.0)
4	131.2 (d)	6.41 (1H, dd, 15.5, 11.0)	131.1 (d)	6.42 (1H, dd, 16.0, 11.0)
5	140.4 (d)	7.11 (1H, d, 15.5)	141.3 (d)	7.10 (1H, d, 16.0)
6	135.8 (s)		135.8 (s)	
7	135.9 (d)	4.37 (1H, d)	136.6 (d)	4.49 (1H, m)
8	30.4 (d)	3.16 (1H, 8.5)	30.4 (d)	3.18 (1H, m)
9	33.3 (t)	1.53 (1H, 4.5)	33.4 (t)	1.53 (1H, m)
		1.81 (1H, m)		1.91 (1H, m)
10	33.5 (d)	1.68 (1H, 4.5)	33.3 (d)	1.76 (1H, m)
11	72.4 (d)	4.37 (1H, d)	73.2 (d)	4.49 (1H, m)
12	140.6 (s)		141.0 (s)	
13	129.5 (d)	7.07 (1H, d, 7.5)	129.5 (d)	7.14 (1H, d, 8.0)
14	127.5 (d)	7.02 (1H, d, 7.5)	128.1 (d)	7.06 (1H, d, 8.0)
15	137.3 (s)		137.2 (s)	
16	20.0 (q)	2.25 (3H, s)	21.3 (q)	2.30 (3H, s)
17	16.9 (q)	1.05 (3H, d, 7.0)	17.7 (q)	1.11 (3H, d, 6.5)
18	23.2 (q)	1.16 (1H, d, 6.5)	24.5 (q)	1.19 (1H, d, 6.5)

concentrations (1,000.00, 500.00, 250.00, 125.00, 62.50, 31.25, 15.63, and 7.81 µg/mL) and a positive control of cisplatin. The samples were incubated for 48 h, followed by the addition of PrestoBlue® reagent. The resulting absorption was read using a multimode reader at 570 nm to determine cell viability and obtain the IC_{50} of the compound.

■ RESULTS AND DISCUSSION

Compound **1** was obtained as a white powder. The molecular formula was determined as $C_{18}H_{22}O_3$ on the HR-TOFMS ion peak at *m/z* 285.1491 $[M-H]^+$ (calcd. for $C_{18}H_{21}O_3$, *m/z* 285.1491) from negative-ion-high-resolution measurements, indicating eight degrees of unsaturation originating from one C=O carboxylic acid, and one aromatic cyclic, two double bonds and one additional cyclic (Fig. S1). The IR spectra showed absorption peaks, which implies the existence of O–H (3266 cm^{-1}), C–H sp^3 (2961 cm^{-1}), C=O (1638 cm^{-1}), and C=C (1599 cm^{-1}) (Fig. S2). The ^1H NMR spectrum showed related to six peaks of signal CH sp^2 resonating at 7.48 (1H, dd, J = 15.5, and 11 Hz,), 7.13 (1H, d, J = 15.5 Hz), 7.07 (1H, d, J = 7.5 Hz), 7.02 (1H, d, J = 7.5 Hz), 6.41 (1H, dd, J = 15.5, and 11 Hz), and 5.92 ppm (1H, d, J = 15.5 Hz). The UV spectrum showed absorption maximum at 208 nm, indicating that a conjugated double bond was likely present in compound **1** (Fig. S3). The J coupling data of this compound showed from the chemical shift that 7.07 and 7.02 ppm have the same J coupling of 7.5 Hz. It shows the ortho position in a benzene ring. Then, this compound has the characteristic of double bonds connected to each other with trans decalin pentanoic acid, which forms compounds such as tanzawaic acid, phompsidin or arohynapene [20-21]. There is one signal of oxymethine resonating at 4.37 ppm and also a signal of CH sp^3 resonating at 3.19 and 1.68 ppm, and a signal of CH_2 sp^3 resonating at 1.81 and 1.53 ppm (each of these shifts has one proton). Then, the spectrum showed three peaks of methyl signals resonating at 1.06, 1.17, and 2.25 ppm (Fig. S4). The ^{13}C-NMR (Table 1, Fig. S5) and DEPT spectra together with HMQC (Fig. S6) analysis revealed a total of 18 carbon signals arising from three methyls at 16.9, 20.0, and 23.2 ppm, one methylene at 33.3 ppm, one oxygenated methine at 72.4 ppm, two methines sp^3 at 30.4 and 33.5 ppm, six methines sp^2 at 120.9, 127.5, 129.5, 131.2, 140.4 and 145.1 ppm, one carbonyl of carboxylic acid at 169.4 ppm, and four quaternary carbon in aromatic ring at 135.8, 135.9, 137.3, and 140.6 ppm.

The HMBC spectra (Fig. S7 & S8) analysis showed the correlation between H-2 (δ_H 5.92 ppm) with C-1 (δ_C 169.4 ppm), H-3 (δ_H 7.48 ppm) with C-1 (δ_C 169.4 ppm)/C-5 (δ_C 140.4 ppm)/C-4 (δ_C 131.2 ppm), H-4 (δ_H 6.41) with C-6 (δ_C 135.8), H-16 (δ_H 2.25) with C-15 (δ_C 137.3)/C-14 (δ_C 127.5), H-13 (δ_H 7.07) with C-7(135.9), H-11 (δ_H 4.37) with C-17 (C-13 (129.5)/C-12 (140.6)/C-9 (33.3)/C-7 (δ_C 135.9)/C-17 (δ_C 16.9), H-17 (δ_H 1.05) with C-9 (δ_C 33.3)/C-11 (δ_C 72.4), and H-18 (δ_H 1.16) with C-9 (δ_C 33.3)/C-8 (δ_C 30.4)/C-7 (δ_C 135.9). The last there is a correlation between H-8 (δ_H 3.16) with C-18 (δ_C 23.3)/C-7 (δ_C 135.9).

Furthermore, the ^1H-^1H COSY experiment (Fig. S9) of compound **1** (bold bonds in Fig. 1(a) & S10) established the key coupling relationships of H-3 (δ_H 7.48) to H-4 (δ_H 6.41)/H-2 (δ_H 5.92), H-5 (δ_H 7.11) to H-4 (δ_H 6.41) which confirmed the position of olefinic moiety outside the benzene ring. Then there is a correlation between H-13 (δ_H 7.07) to H-14 (δ_H 7.02) confirmed the *ortho* position to each other in a benzene ring, H-8 (δ_H 3.16) correlated to H-18 (δ_H 1.16)/H-9 (δ_H 1.53) and H-10 (δ_H 1.68) to H-9 (δ_H 1.53)/H-17 (δ_H 1.05). This partial structure was also reinforced by the HMBC correlation so that compound **1** was identified as arohynapene A as shown in Fig. 1(a) & S10. A NOESY experiment (Fig. S11) was conducted to determine the relative configuration at the stereocenters in compound **1** (Fig. 1(b) & S12). The α-orientation of H-8 was established by J coupling value as much as 4.5 Hz. The NOESY spectrum shows that H-11 correlated with H-10, and H-8 correlated with H-10 so that H-8, H-10, and H-11 clearly suggested the co-facial orientations of these protons with α-orientation and confirmed the two methyls at C-8, C-10, and hydroxyl at C-11 were β-oriented. This compound is also compared to the absolute structure of arohynapene A compound (Fig. S13), which shows similarities where the positions H-8, H-10 and H-11 are in the alpha position [21].

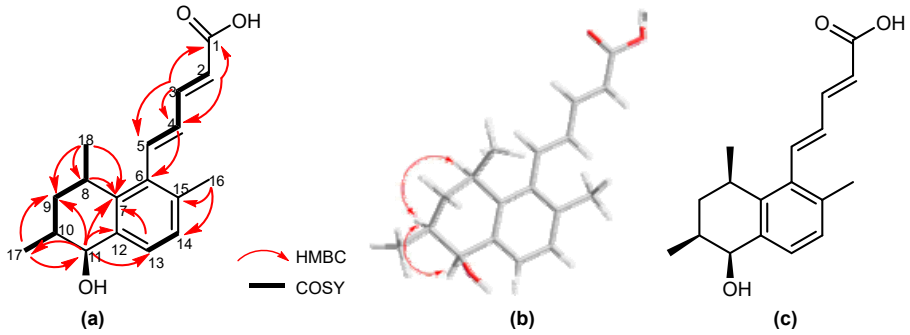

Fig 1. (a) Selected HMBC and ^{1}H-^{1}H COSY correlations of compound **1**, (b) selected ^{1}H-^{1}H NOESY correlations of compound **1**, and (c) the chemical structure of compound **1** as arohynapene A

Based on the spectroscopic analysis, compound **1** was identified as arohynapene A as shown in Fig. 1(c) & S14. This result was supported by the comparison between literature as shown in Table 1, where this compound has previously been isolated from the endophytic fungi *Penicillium* sp. FO-2995 derived from a water sample in Tanegashima, Kagoshima, Japan, and anticoccidial activity with MIC 35.0 µM [20-23].

The cytotoxic activities of compound **1** showed no significant activities against four cancer cell lines such as HeLa cervical, MCF 7 breast cancer, B16-F10 melanoma, and lung adenocarcinoma A549 cells (IC_{50} values > 500 µg/mL). Cisplatin was used as a positive control and had IC_{50} 19 µg/mL. These results suggested that the long chain of aliphatic can reduce cytotoxic activity.

■ CONCLUSION

Arohynapene A (**1**) has been isolated from *Penicillium steckii* JB-NW-2-1, endophytic fungi derived from mangrove plant *A. marina* (Forssk) Vierh. Compound **1** showed no cytotoxic activities against HeLa cervical, MCF 7 breast, B16-F10 melanoma, and A549 lung adenocarcinoma cancer cell lines (IC_{50} values > 500 µg/mL).

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■ SUPPORTING INFORMATION

This article has an attachment with the supporting information.

■ CONFLICT OF INTEREST

The authors declare no conflict of interest.

■ AUTHOR CONTRIBUTIONS

Conceptualization, Yeni Mulyani, Asri Peni Wulandari and Unang Supratman; methodology, Wahyu Safriansyah, Azmi Azhari, Sari Purbaya, and Fajar Fauzi Abdullah; validation, Unang Supratman, and Asri Peni Wulandari; formal analysis, Aprilia Permata Sari, Galih Bayu Pratama, Fajar Fauzi Abdullah, and Kindi Farabi; investigation, Yeni Mulyani, Asri Peni Wulandari, and Unang Supratman; resources, Kindi Farabi and Azmi Azhari; data curation, Yoshihito Shiono; writing—original draft preparation, Yeni Mulyani, and Wahyu Safriansyah; writing—review and editing, Aprilia Permata Sari, Kindi Farabi and Unang Supratman; supervision, Yoshihito Shiono, Asri Peni Wulandari, and Unang Supratman; project administration, Yoshihito Shiono, and Unang Supratman; funding acquisition, Unang Supratman. All authors have read and agreed to the published version of the manuscript.

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