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Antioxidant neolignans from the twigs and leaves of Mitrephora wangii HU

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Abstract

Two new compounds, odoratisol E (1) and decurrenal A (2), together with 12 known compounds were isolated from the twig and leaf extracts of *Mitrephora wangii* HU (Annonaceae). All structures were elucidated by spectroscopic methods. The structure of compound (+)-6 was also confirmed by X-ray diffraction analysis. The absolute configurations of odoratisol E and decurrenal A were determined by comparison of their electronic circular dichroism (ECD) spectra with those of related known compounds. Most of the isolated compounds were evaluated for their antioxidant activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assays. Compounds 4 and (+)-6 displayed potent ABTS radical scavenging activity with IC_{50} values of 11.9 ± 1.8 and 10.8 ± 1.7 μM, respectively, which is better than that of standard compound, ascorbic acid, (IC_{50} = 19.3 ± 0.1 μM). Compound 9 showed moderate DPPH radical scavenging activity with an IC_{50} value of 38.7 ± 0.8 μM.

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Antioxidant neolignans from the twigs and leaves of *Mitrephora wangii* HU

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ABSTRACT

Two new compounds, odoratisol E (**1**) and decurrenal A (**2**), together with 12 known compounds were isolated from the twig and leaf extracts of *Mitrephora wangii* HU (Annonaceae). All structures were elucidated by spectroscopic methods. The structure of compound (+)-**6** was also confirmed by X-ray diffraction analysis. The absolute configurations of odoratisol E and decurrenal A were determined by comparison of their electronic circular dichroism (ECD) spectra with those of related known compounds. Most of the isolated compounds were evaluated for their antioxidant activity using the 2,2-diphenyl-1-pikrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assays. Compounds **4** and (+)-**6** displayed potent ABTS radical scavenging activity with IC_{50} values of 11.9 ± 1.8 and 10.8 ± 1.7 µM, respectively, which is better than that of standard compound, ascorbic acid, (IC_{50} = 19.3 ± 0.1 µM). Compound **9** showed moderate DPPH radical scavenging activity with an IC_{50} value of 38.7 ± 0.8 µM.

Keywords: *Mitrephora wangii*, Annonaceae, lignan, neolignan, antioxidant activity

1. Introduction

Free radicals, especially oxygen derived radicals produced from exogenous and endogenous metabolic processes in the human body, are the cause of various diseases including cirrhosis, arteriosclerosis, rheumatoid arthritis, cancer, inflammatory diseases, and neurodegenerative diseases associated with aging [1–4]. An imbalance between the formation and neutralization of free radicals results in diseases and the acceleration of aging [1, 2]. Normally, the human body has several mechanisms to protect cells, including enzymes such as superoxide dismutase or catalase or antioxidant compounds such as ascorbic acid, tocopherol, and glutathione [1–3]. There are several literature reports that natural antioxidants play crucial roles in the prevention or reduction of the risks of chronic diseases as well as in the maintenance or promotion of a state of well-being or health [5–7]. Plant secondary metabolites such as flavonoids, neolignans, and terpenoids also play an important role in the defense against free radicals. In addition, benzofuran-type neolignans exhibit a significant inhibitory effect against lipid peroxidation [8]. Therefore, the discovery of active antioxidants from natural resources has received much attention.

Mitrephora belongs to the Annonaceae family and approximately 48 species are distributed throughout Asia and Australia. In Thailand, twelve species are found and some of these have been used in Thai traditional medicine as health tonics [9,10]. Previous phytochemical investigations of *Mitrephora wangii* HU twigs and leaves resulted in the isolation and identification of neolignans, alkaloids, phenolic amides, and steroids, and allantoin. Some of these compounds showed antifungal, cytotoxic, and antioxidant activities [11–17]. The objective of the present study was to evaluate the antioxidant potential and to establish phytochemical characterization of the secondary metabolites isolated from the twig and leaf extracts of *M. wangii*. Herein, we report two new compounds (**1** and **2**) together with

12 known compounds (**3**–**14**) from the twig and leaf extracts of *M. wangii*. The antioxidant activities, DPPH and ABTS assays, of most of these compounds are also reported.

2. Results and discussion

The EtOAc extract of the leaves of *M. wangii* was separated by column chromatography (CC) using various stationary phases to yield two previously undescribed compounds (**1** and **2**) together with four known compounds (**11**–**14**). While the separation of the EtOAc extract of the twigs yielded eight known compounds (**3**–**10**).

Compound **1** was obtained as a colorless oil with a molecular formula of $C_{19}H_{22}O_3$ based on the $[M + Na]^+$ ion peak at *m/z* 321.1469 (calcd for $C_{19}H_{22}O_3Na$, 321.1469) from HRESITOFMS. The ^{1}H NMR spectroscopic data of **1** (Table 1) displayed resonances for the presence of two benzylic oxymethines [δ_H 5.13 (1H, d, *J* = 8.7 Hz, H-7), 4.37 (1H, d, *J* = 9.3 Hz, H-7′)], two methines [δ_H 2.23 (1H, m, H-8), 1.74 (1H, m, H-8′)], two methyl groups [δ_H 1.02 (3H, d, *J* = 6.5 Hz, H-9′), 0.63 (3H, d, *J* = 6.9 Hz, H-9)], two aromatic rings having an AA′BB′ spin system [δ_H 7.37 (2H, d, *J* = 8.4 Hz, H-2′/6′), 7.31 (2H, d, *J* = 8.4 Hz, H-2/6), 6.88 (2H, d, *J* = 8.4 Hz, H-3/5), 6.85 (2H, d, *J* = 8.4 Hz, H-3′/5′)] and a methoxy group [δ_H 3.81 (3H, s, OMe-4)]. The ^{13}C NMR spectroscopic data revealed resonances, representing 19 carbons including, 12 aromatic carbons, four methine carbons, and three methyl carbons. The NMR spectroscopic data of **1** were similar to those of (7*S*,8*R*,7′*R*,8′*S*)-4′-hydroxy-4-methoxy-7,7′-epoxylignan (**15**) isolated from *Terminalia superba* by Wansi *et al.* in 2007 (Table 1). The major differences between these two compounds were observed from the following NMR spectroscopic data of the furan. The two methyl groups of **15** have a *syn* relationship with resonances at δ_H 0.55 (3H, d, *J* = 5.7 Hz, Me-9)/δ_C 11.8 and δ_H 0.57 (3H, d, *J* = 5.7 Hz, Me-9′)/δ_C 11.8 [18], whereas in compound **1** the methyl groups are *anti* and resonate at δ_H 0.63 (3H, d, *J* = 6.9 Hz, Me-9)/δ_C 14.4 and 1.02 (3H, d, *J* = 6.5 Hz, Me-9′)/δ_C 14.4. The protons and carbons at C-7 and C-7′ of compound **15** are magnetically equivalent and

resonance at δ_H 5.10 (2H, d, J = 5.8 Hz, H-7 and H-7′)/δ_C 82.6, while the ^{1}H and ^{13}C NMR spectra of compound **1** displayed two set of resonances, δ_H 5.13 (1H, d, J = 8.7 Hz, H-7)/δ_C 82.3 and δ_H 4.37 (1H, d, J = 9.3 Hz, H-7′)/δ_C 86.7. The *cis/trans* relationship of the tetrahydrofuran substituents were determined from the resonances of oxymethine (H-7/7′) and methyl protons as described by Giang *et al*. in 1994 [19] and Rimando *et al*. in 2006 [20]. The NOESY cross peaks of **1** between Me-9′ (δ_H 1.02) with H-7′ (δ_H 4.37) and H-7 (δ_H 5.13) with H-8 (δ_H 2.23) supported these assignments. Finally, the absolute configuration of **1** was established as 7*S*,8*R*,7′*R*,8′*R* by comparison of its specific rotation and ECD spectrum with those of odoratisol C (**16**) and odoratisol D (**17**) (Fig. 1 and 3) [20]. Thus, the structure of odoratisol E ((7*S*,8*R*,7′*R*,8′*R*)-4′-hydroxy-4-methoxy-7,7′-epoxylignan) was assigned as **1**, the C-8′ epimer of **15**.

Compound **2** was obtained as a colorless viscous oil. The molecular formula of $C_{16}H_{14}O_4$ was established on the basis of HRESITOFMS data, which showed a $[M + H]^+$ ion peak at *m*/*z* 271.0967 (calcd for $C_{14}H_{15}O_4$, 271.0970). The ^{1}H and ^{13}C NMR spectroscopic data (Table 2) of **2** were similar to those of **3** [21], except compound **2** showed resonances for an ABX aromatic spin system [δ_H 6.58 (1H, s, H-2′/δ_C 105.2), δ_H 6.47 (1H, d, J = 7.2 Hz, H-5′/δ_C 106.7), and δ_H 6.60 (1H, d, J = 7.2 Hz, H-6′/δ_C 115.6)] instead of the AA′BB′ aromatic spin system observed in the ^{1}H NMR spectrum of **3**. The *2S*,*3S* absolute configuration of **2** was identified from a comparison of its ECD spectrum with that of compound **3** [22] (Fig. 4) and compound (+)-**6**; whose structure was determined by X-ray crystallographic analysis (Fig. 5). Thus, the structure of decurrenal A ((*2S,3S*)-2,3-dihydro-2-(3′,4′-dihydroxyphenyl)-3-methyl-5-benzofurancarboxaldehyde) was assigned as **2**.

The remaining known compounds were identified as decurrenal (**3**) [21], parakmerin A (**4**) [23], (–)-licarin A (**5**) [24, 25], (+)-conocarpan (**6**) [21, 23, 26], (2*S*,3*S*)-2,3-dihydro-2-(3,4-dimethoxyphenyl)-3-methyl-5-(*E*)-propenylbenzofuran (**7**) [22], eupomatenoid-4 (**8**)

[27], eupomatenoid-5 (**9**) [21], eupomatenoid-6 (**10**) [27], *threo*-1-(4-hydroxypheny)-2-[4-(*E*)-propenylphenoxy]-propan-1-ol (**11**) [28], *erythro*-1-(4-hydroxypheny)-2-[4-(*E*)-propenylphenoxy]-propan-1-ol (**12**) [23], *N*-cinnamoyl-(2-phenylethyl)-amine (**13**) [29], 4-hydroxy-benzaldehyde (**14**) [30] by comparing their spectroscopic data with those previously reported.

Most of the isolated compounds, as well as the crude extracts, were evaluated for their antioxidant activities using the DPPH and ABTS radical-scavenging assays. As summarized in Table 3, compounds **4** and (+)-**6** showed potent ABTS radical scavenging activities with IC_{50} values of 11.9 ± 1.8 and 10.8 ± 1.7 µM, respectively, a result nearly two-fold more potent than the standard, ascorbic acid, (IC_{50} = 19.3 ± 0.1 µM), whereas compounds **3**, **5**, and **9** showed moderate ABTS radical scavenging activity with IC_{50} values of 33.9 ± 2.6, 36.7 ± 1.0, and 48.4 ± 2.9 µM, respectively. It should be noted that the formyl group at C-5 (compound **3**), the methoxy group at C-7 (compound **5**), and the double bond at C-2/C-3 (compound **9**) may cause the reduction of antioxidant activity of neolignans. In the DPPH radical-scavenging assay, all tested compounds were either weakly active or inactive. The crude extract and some of the isolated compounds were also evaluated for their α-glucosidase inhibitory activities. Unfortunately, none of them were active.

3. Experimental

3.1. General experimental procedures

The NMR spectra were recorded using a 400 MHz Bruker FT-NMR Ultra Shield or a Bruker Avance 600 MHz spectrometer. Optical rotation values were determined on a JASCO P-1010 polarimeter in MeOH solution by using a glass cell (3.5 × 10 mm). UV absorption spectra were obtained on Varian Cary 5000 UV–vis-NIR spectrophotometer. The IR spectra were recorded using a Perkin-Elmer FTS FT-IR spectrophotometer. ECD spectra were taken on a JASCO J-815 CD spectropolarimeter. ESIMS and ESITOFMS spectra were obtained on

156 a Bruker HCT Ultra mass spectrometer and Waters Micromass LCT mass spectrometer.
157 Semi-preparative HPLC was performed on a Waters 1525 HPLC pump system, equipped
158 with a Waters 2487 dual wavelength absorbance detector using the following column:
159 Phenomenax Luna 5μ C_8 column (5 μm, 10 × 250 mm). Single-crystal X-ray diffraction
160 measurements were made on a Bruker APEX DUO diffractometer with cross-coupled
161 multilayer optics Cu-Kα radiation. Quick column chromatography (QCC) and column
162 chromatography (CC) were carried out on Si gel 60 H (Merck, 5–40 μm) and Si gel 100
163 (63–200 μm, Merck) or silica gel 100 (63–200 μm, SiliCycle® Inc.) or Silica gel RP-18
164 (55–105 μm, Waters), respectively. Precoated plates of silica gel 60 F_{254} and RP-18 F_{254} were
165 used for analytical purposes. Silica gel plates (Merck, silica gel 60 F_{254}) were used for
166 preparative TLC. Sephadex LH-20 (Merck) was used as a stationary phase for size-exclusion
167 chromatography. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) was used as a substrate in the DPPH
168 assay. 2,2′-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) was used as a substrate
169 and ABTS radical cations were generated by potassium persulfate ($K_2S_2O_8$) in the ABTS
170 assay. DPPH and ABTS assays were performed on a BMG LABTECH/SPECTROstar Nano
171 microplate reader.

172 *3.2. Plant materials*

173 The twigs and leaves of *Mitrephora wangii* were collected from Doi Tung, Chiang
174 Rai Province, Thailand, in October 2015. The plant material was authenticated by Mr. Martin
175 van de Bult (Doi Tung Development Project, Chiang Rai, Thailand), and a voucher specimen
176 (MFU-NPR0127) was deposited at the Natural Products Research Laboratory, School of
177 Science, Mae Fah Luang University.

178 *3.3. Extraction and isolation*

179 Air-dried twigs of *M. wangii* (17.2 kg) were extracted three times with EtOAc (3 L
180 each) for 3 days at room temperature. After concentrated under reduce pressure, the EtOAc

extract (211.0 g) was subjected to quick column chromatography (QCC) over silica gel, eluting with a gradient of *n*-hexane-acetone (1:0 to 0:1, v/v) to provide seventeen fractions (A–Q). Fraction F (755.5 mg) was fractionated on silica gel chromatography (CC) eluted with *n*-hexane-CH_2Cl_2 (17:3, v/v) to afford seven subfractions (F1–F7). Subfraction F4 (193.0 mg) was purified further by silica gel CC eluted with *n*-hexane-EtOAc (1:1, v/v) to give compound **8** (2.0 mg). Fraction H (2.12 g) was fractionated over Sephadex LH-20 CC (eluted with MeOH) to afford six subfractions (H1–H6). Subfraction H5 (915.9 mg) was further purified by silica gel CC [eluted with *n*-hexane-acetone (9:1, v/v)] to afford compound **7** (7.3 mg). Compound **9** (8.7 mg) was obtained from subfraction H6 (154.5 mg) by using MeOH as eluent on a Sephadex LH-20 column. Fraction I (1.5 g) was purified via silica gel CC (eluted with *n*-hexane-acetone (9:1, v/v)) to give compound **4** (404.6 mg). Fraction K (2.7 g) was further purified by Sephadex LH-20 CC (eluted with MeOH) followed by silica gel CC (eluted with *n*-hexane-EtOAc (9:1, v/v)) to yield compounds **5** (3.6 mg) and **6** (304.3 mg). Fraction L (4.5 g) was subjected to QCC (eluted with *n*-hexane-acetone mixture of increasing polarities (9:1 to 1:1, v/v)) to yield ten subfractions (L1-L10). Fraction L4 (435.8 mg) was further purified by Sephadex LH-20 CC (eluted with MeOH) to give seven subfractions (L4A-L4G). Compound **3** (6.0 mg) was obtained from fraction L4C (104.8 mg) via silica gel CC (eluted with *n*-hexane-EtOAc (4:1, v/v)). Compound **10** (2.3 mg) was obtained from fraction L4E after preparative TLC with *n*-hexane-CH_2Cl_2 (4:1, v/v).

The dried leaves of *M. wangii* (6.4 kg) were extracted with EtOAc (3 L each) for 3 days at room temperature to afford the crude extract (119.8 g), which were subjected to QCC over silica gel, eluting with a gradient of *n*-hexane-acetone (0:1 to 1:0, v/v), providing 10 fractions (A–J). Fraction H (7.37 g) was fractionated over QCC eluting with a gradient of *n*-hexane-EtOAc (0:1 to 1:1, v/v) to give ten subfractions (H1-H10). Subfraction H4 (102.3 mg) was further purified by silica gel CC (eluted with *n*-hexane-acetone (4:1, v/v)) following

206 separation by CC over silica gel RP-18 column eluting with MeOH-H_2O (4:1, v/v) to yield
207 compound **11** (1.5 mg). Subfraction H6D2 (14.8 mg) was purified by semi-preparative HPLC
208 (eluted with CH_3CN/H_2O with 0.05% TFA, 7:3, 2 mL/min) to obtain compound **1** (1.0 mg, t_R
209 = 21.4 min). Fraction I (13.4 g) was subjected to QCC over silica gel (eluted with *n*-hexane-
210 acetone gradient (1:0 to 7:3, v/v)) to provide eleven subfractions (I1-I11). Subfraction I4
211 (740.0 mg) was purified by silica gel CC (eluted with *n*-hexane-acetone (9:1, v/v)) to afford
212 seven subfractions (I4A-I4G). Subfraction I4D (173.1 mg) was isolated by Sephadex LH-20
213 CC (eluted with MeOH) and further purified by semi-preparative HPLC (eluted with
214 CH_3CN/H_2O with 0.05% TFA, 1:1, 2 mL/min) to give compounds **2** (1.2 mg, t_R = 14.9 min),
215 **12** (1.1 mg, t_R = 29.4 min), **13** (0.5 mg, t_R = 28.0 min), and **14** (1.0 mg, t_R = 10.1 min).

216 Odoratisol E (**1**): colorless oil; $[\alpha]^{22}_D$: – 49.7 (*c* 0.6, MeOH); UV (MeOH) λ_{max} (log ε)
217 214 (2.95), 229 (2.79), 275 (2.33) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 213 (–1.74), 228 (+0.76), 279
218 (+0.088) nm; IR (neat) υ_{max} 3310, 2958, 1610, 1512, 1452, 1241 cm^{-1}. ^1H NMR ($CHCl_3$, 600
219 MHz) and ^{13}C NMR ($CHCl_3$, 150 MHz) see Table 1; HRESITOFMS: *m/z* 321.1469 [M +
220 Na]$^+$ (calcd for $C_{19}H_{22}O_3Na$, 321.1467).

221 Decurrenal A (**2**): colorless oil; $[\alpha]^{25}_D$: + 27.0 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log
222 ε) 224 (2.65), 291 (2.5) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 234 (–0.85), 291 (+0.89) nm; IR (neat)
223 υ_{max} 3362, 2923, 2853, 1673 cm^{-1}. ^1H NMR (acetone-d_6, 600 MHz) and ^{13}C NMR (acetone-
224 d_6, 150 MHz) data, see Table 2; HRESITOFMS *m/z* 271.0967 [M + H]$^+$ (calcd for $C_{16}H_{15}O_4$,
225 271.0970).

226 X-ray crystallographic data for (+)-conocarpan (**6**): $C_{18}H_{18}O_2$, *M* = 266.32, size 0.13 ×
227 0.24 × 0.34 mm^3, orthorhombic, chiral group $P2_12_12_1$, *a* = 8.8705 (3) Å, *b* = 8.9317 (3) Å, *c* =
228 18.0613 (6) Å, $\alpha = \beta = \gamma = 90.00^o$, *V* = 1430.97 (8) $Å^3$, *T* = 89.95 K, *Z* = 4, *d* = 1.236 g/cm^3,
229 *F*(000) = 568.00, λ (CuKα) = 1.54178 Å, reflections collected/unique 9,812/2,522 [*R* (int) =
230 0.027]. Final *R* indices R_1= 0.027 and wR_2 = 0.064 ($I > 2\sigma(I)$), R_1 = 0.028 and wR_2 = 0.065

(all data), GOF = 1.07, largest diff. peak/hole, 0.20/–0.14 $e^-/Å^3$. The absolute configurations of compound (+)-**6** was assigned as 2*S*, 3*S* (Fig. 5) with a Flack parameter was –0.11(8). Data were collected on Bruker APEX DUO diffractometer using Cu-Kα radiation. The crystallographic data of (+)-**6** have been deposited in the Cambridge Crystallographic Data Centre as CCDC 1839325 and data can be obtained free of charge from the via http://www.ccdc.cam.ac.uk/data_request/cif.

3.4 Assay for DPPH radical-scavenging activity

The DPPH scavenging activity assay was modified from a previous paper [31]. Briefly, 6×10^{-5} M DPPH was prepared in absolute EtOH, and then 100 µL of this solution was mixed with 100 µL of sample solution in a 96-well microplate. After 30 min of the reaction in the absence of light at room temperature, the absorbance was measured using microplate reader (SPECTROstar Nano) at 517 nm. The DPPH radical scavenging capacity was calculated using the following equation. % inhibition = $[(A_B - A_S)/A_B] \times 100$ where A_B and A_S are the absorbance of the blank sample and sample, respectively. All experiments were performed in triplicate, with ascorbic acid used as the positive control. The half maximal inhibitory concentration (IC_{50}) of DPPH scavenging activity was calculated by plotting inhibition percentages against concentrations of the sample. The inhibition values were reported as means ± SD.

3.5. Assay for ABTS radical-scavenging activity

The determination of $ABTS^{\bullet+}$ scavenging activity was carried out using a modified literature procedure [31]. $ABTS^{\bullet+}$ were produced by reacting a 7 mM stock solution of ABTS with 2.45 mM potassium persulfate ($K_2S_2O_8$) and allowing the mixture to stand in the dark at room temperature for 16 h before use. The $ABTS^{\bullet+}$ solution was diluted with water to an absorbance of 0.7 ± 0.02 at 734 nm. Different concentrations of test samples (20 µL) and $ABTS^{\bullet+}$ solution (180 µL) were added to each well of the 96-well microplate. The absorbance

at 734 nm was determined after 5 min of mixing. The percentage of ABTS free radical scavenging activity was calculated using the same formula as for the DPPH assay. The measurements were performed in triplicate.

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Appendix A. Supplementary data

Supplementary data of compounds **1** and **2**, X-ray diffractions data of (+)-**6** associated with this article can be found in the online version, at

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