

The Limonoids and Other Constituents from the Fruits of *Melia azedarach* and Their Biological Activity

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(Received June 10, 2021; Revised August 10, 2021; Accepted August 15, 2021)

Abstract: Eleven chemical constituents, including one new limonoid trichilinin G (**1**), were identified from the fruit extracts of *M. azedarach*. The structure of **1** was established by various spectroscopic and mass spectrometric analyses. Among the eleven isolated compounds, trichilinin G (**1**) and meliatoxin B1 (**2**) were examined for their antifungal activity against *Fusarium oxysporum*, *Magnaporthe grisea*, *Phytophthora* spp. (PS), and *P. capsici* (PC). Limonoid **2** showed the best antifungal activity against PS (IC₅₀ = 103.8 µg/mL) and PC (IC₅₀ < 62.5 µg/mL) in a dose-dependent manner. While limonoid **1** exhibited a weak to moderate activity against these *Phytophthora* species, *F. oxysporum* and *M. grisea* were less sensitive to the two compounds tested. The inhibitory effects of trichilinin G on superoxide anion generation and elastase release by human neutrophils were also assessed in cellular model and did not show significant activity.

Keywords: Triterpenoid; limonoid; trichilinin; antifungal; anti-inflammatory. © 2021 ACG Publications. All rights reserved.

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1. Introduction

Melia azedarach L. (Meliaceae) is widely distributed in Vietnam and well known for its control of nematode pests, mites, and insects. The dried leaves, fruits, barks, seeds and roots of *M. azedarach* L. have shown to contain various compounds including limonoids, triterpenoids, steroids, alkaloids, and flavonoid glycosides [1], which display broadband medicinal characteristics, among these the insecticidal activities against several pathogenic and pest organisms were most recognized [2]. Moreover, *M. azedarach* was reported a broadband spectrum of bioactivities, such as antibacterial, antifungal, antiviral, anti-fertility, anti-malarial, hepatoprotective, antioxidant and anticancer effects [3-6]. Until now, there were many reported research results regarding *M. azedarach*. However, the fruits of *M. azedarach* still attract the attention of scientists, which prompted us to conduct this research. In our research about genus *Melia*, we reported the structure of a limonoid trichilin G (**1**). Moreover, the identification of ten known compounds (**2-11**) were provided in this study.

2. Materials and Methods

2.1. General Experimental Procedures

The UV spectra were recorded on Hitachi U-0080D diode array spectrophotometer. The IR spectra were recorded on PerkinElmer FT-IR Spectrum RX1 spectrophotometer. Melting points were recorded on Yanagimoto MP-S3. Optical rotations were recorded on a Jasco P-2000 digital polarimeter. The NMR spectra (¹H- and ¹³C-NMR, COSY, NOESY, HMQC, and HMBC) were determined using the Bruker AV-III 500 NMR spectrometer. The ESIMS and HRESIMS were recorded on Bruker Daltonics APEX II 30e spectrometer (positive-ion mode).

2.2. Plant Materials

The fruits of *M. azedarach* identified by Dr. Quoc Binh Nguyen, Vietnam National Museum of Nature, Vietnam Academy of Science and Technology, Hanoi, Vietnam. In July 2018, it were collected at the Puhuong nature reserve, Nghean province, Vietnam. A voucher specimen (No. MAF-072018) was deposited at the School of Chemistry, Biology and Environment, Vinh University, Vietnam.

2.3. Extraction and Isolation

Air-dried fruits of *M. azedarach* (4.0 kg) were extracted with methanol using sonicator to afford a crude methanol (350 g). The crude methanol was suspended in water and partitioned successively with *n*-hexane, dichloromethane, and ethyl acetate to give corresponding *n*-hexane (MAH, 62 g), dichloromethane (MAD, 48 g), ethyl acetate (MAE, 45 g) and water (MAW, 95 g) layers, respectively. The MAE fraction was subsequently chromatographed on a silica gel column eluting with *n*-hexane/ethyl acetate (100/1 to 0/1, v/v) to afford seven fractions (MAE 1-7). The MAE 1 fraction (2.3 g) was further separated on a silica gel column eluting with *n*-hexane/ethyl acetate (25/1, v/v) to yield two subfractions (MAE 1.1 and 1.2). Compound **1** (5 mg) was yielded from MAE 1.1 subfraction (0.3 g) purified by a RP-18 column eluting with methanol/water (9/1, v:v). The MAE 1.2 subfraction (0.2 g) was chromatographed with the assistance of a silica gel column (150 g, 80 × 3 cm) eluting with a mixture of *n*-hexane/acetone (15:1) to afford compound **9** (128 mg). Moreover, the MAE 1.2 subfraction was further separated on a Sephadex LH-20 column eluting with methanol/water (1/1, v/v) to produce compound **6** (28 mg) and compound **8** (31 mg). The MAE 2 fraction (0.9 g) was repeatedly chromatographed on a RP-18 column eluting with methanol/water (3/1, v/v) to result in compound **5** (7 mg). The MAE 2 (16.5 g) was further separated on a silica gel column eluting with *n*-hexane:ethyl acetate (10/1 to 2/1) to yield six subfractions (MAE2.1-MAE2.6). The MAE 2.2 subfraction was chromatographed with the assistance of a silica gel column (150 g, 80 × 3 cm) eluting with a mixture of *n*-hexane/acetone (6/1) to yield compound **3** (18 mg). The MDE2.4 purified by HPLC eluting with CH₃CN/H₂O (40:60 to 85:15) to afford compound **2** (6 mg) and compound **4** (7,4 mg). The MAE 5 (1.3

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g) was purified by silica gel column chromatography (200 g, 80 × 3 cm) eluting with a mixture of chloroform and methanol (10:1) to yield compound **7** (51 mg).

The dichloromethane layer (MAD, 48 g) was subsequently chromatographed on a silica gel column eluting with *n*-hexane/ethyl acetate (step gradient 30/1, 20/1, 10/1, 4/1, 2/1, 1/1, successively; v/v) to afford five fractions (MAD 1-5). The MAD 2 fraction (1.7 g) was isolated by silica gel column chromatography eluting with chloroform/methanol (10/1) to yield compound **11** (25 mg). The MAD 5 fraction (1.5 g) was chromatographed with the assistance of a silica gel column (200 g, 80 × 3 cm) eluting with a mixture of chloroform and methanol (10:1) to produce compound **10** (41 mg).

2.3.1. *Trichilin G (I)*

White powder, mp 115-117 °C; $[\alpha]_D^{25} +31.5$ (*c* 0.07, CHCl₃); UV (MeOH) λ_{\max} (log ϵ) 273 (3.23), 244 (3.53), 218 (3.13), 205 (3.17) nm; IR ν_{\max} : 3590, 1731, and 1600-1500 cm⁻¹; ¹H- and ¹³C-NMR, see Table 1; ESI-MS (*rel. int.*) *m/z* 655 ([M+Na]⁺, 100), 633 (35); HR-ESI-MS *m/z*: 655.2879 [M+Na]⁺ (calcd. for C₃₇H₄₄O₉Na, 655.2878).

Table 1. ¹H-NMR (500 MHz, CDCl₃) and ¹³C-NMR (125 MHz, CDCl₃) of **1**

Position	δ_H (ppm, multi., <i>J</i> in Hz)	δ_C (ppm)
1	3.56 (br s)	71.8
2	1.53 (m), 2.27 (m)	24.3
3	3.56 (br s)	72.8
4	-	42.3
5	2.55 (d, 12.5)	40.3
6	4.27 (dd, 12.5, 3.0)	73.6
7	5.85 (d, 3.0)	74.2
8	-	51.7
9	3.15 (dd, 13.0, 7.5)	36.2
10	-	44.1
11	2.04 (m), 2.36 (m)	30.0
12	5.08 (m)	77.8
13	-	40.2
14	-	155.7
15	5.70 (br s)	122.7
16	2.32 (m)	36.6
17	2.97 (dd, 10.8, 7.5)	50.4
18	1.18 (s)	18.8
19	3.13 (m), 3.45 (d, 7.5)	77.9
20	1.00 (s)	15.8
21	1.25 (s)	27.1
22	1.00 (s)	15.4
23	-	124.6
24	7.13 (br s)	140.2
25	7.28 (br s)	141.9
26	6.16 (br s)	111.8
27	-	169.0
28	1.91 (s)	20.8
29	-	171.0
30	1.90 (s)	21.3
1'	-	165.0
2'	-	130.6
3'	8.08 (d, 7.5)	129.5
4'	7.43 (t, 7.5)	128.3
5'	7.56 (t, 7.5)	132.9
6'	7.43 (t, 7.5)	128.3
7'	8.08 (d, 7.5)	129.5

2.4. Anti-inflammatory Bioactivity Examination

The assays of the generation of superoxide anion and elastase release inhibition examinations were determined as described previously [7,8].

2.5. *In vitro* Antifungal Activity Bioassays

The isolated compounds **1** and **2** were tested for their *in vitro* antifungal activity against four phytopathogenic fungi *Fusarium oxysporum*, *Magnaporthe grisea*, *Phytophthora* spp., and *P. capsici* by poisoned-food technique. In brief, the tested compounds were dissolved with 2% DMSO and then added to melted PDA medium at 50 °C in Petri dishes, let the dishes cooling at room temperature. The isolated compounds **1** and **2** were treated in a range concentration of (62.5-500 µg/mL). The treated Petri dishes were inoculated with a mycelial plug in the center and allowed to grow at 25–28 °C for 2–7 days. The Petri dishes treated with 2% DMSO were used as negative controls. Antifungal assays were performed at least twice. The percentage of mycelial inhibition (%) was calculated based on the Abbott's formula: % control = 100 x [(A – B)/(A – 4)]

where A: diameter of the mycelial growth of negative control (mm); B: diameter of mycelial growth of treatment (mm); 4: diameter of PDA plug of fungal inoculum (mm).

The data were evaluated by one-way ANOVA and the significance of the treatments was determined by Tukey's HSD for multiple comparisons ($P \leq 0.05$). The half-maximal inhibitory concentration (IC₅₀, µg/mL) of the tested compounds against the mycelial growth was calculated by Probit analysis of WINPEPI software version 11.63.

3. Results and Discussion

Compounds **1–11** were purified with the combination of conventional chromatographic techniques and the structure of new compound **1** was elucidated as below. Compound **1** was isolated as optically active colorless syrup and the HRESIMS analytical data of **1** revealed the molecular formula as C₃₇H₄₄O₉ (m/z 655.2879 for [M+Na]⁺). The UV absorption maxima at 205, 218, 244, and 273 nm indicated the presence of a conjugated benzene chromophore [9]. The IR absorptions at 3590, 1731, and 1600-1500 cm⁻¹ were indicative of the presences of hydroxyl, ester, and olefinic double bond functionalities. The ¹H-NMR spectrum of **1** (Table 1) displayed the characteristic resonances for four methyl singlets [δ_H 1.00 (6H, CH₃-20, -22), 1.18 (3H, CH₃-18), and 1.25 (3H, CH₃-21)], one oxymethylene group [δ_H 3.13 (m) and 3.45 (d, $J = 7.5$ Hz)], and one set of signals for furan moiety [δ_H 6.16 (br s), 7.13 (br s), and 7.28 (br s)], respectively, which indicated the basic skeleton of **1** was similar to that of trichilins [10]. In addition, there were also proton signals representative for two acetyl singlets [δ_H 1.90 (3H) and 1.91 (3H)] and one benzoyl fragment [δ_H 7.43 (2H, t, 7.5), 7.56 (1H, t, 7.5), and 8.08 (2H, d, 7.5)]. Comparison of the above spectral data with those of trichilin E [11], the observed difference in **1** was the presence of one more acetyl group. The substitution position of acetyl and benzoyl groups were determined by the assistance of comprehensive 2D NMR spectroscopic examinations of **1**. In the HMBC spectrum, ²J, ³J-HMBC correlations from H-3 to C-1, C-27; from H-6 to C-7; from H-7 to C-1'; from H-12 to C-29; from H-15 to C-8, C-17; from H-17 to C-23, C-24, C-26; from CH₃-18 to C-3, C-4, C-19; from CH₃-20 to C-1, C-5, C-9; from CH₃-21 to C-14; from CH₃-22 to C-12, C-14, C-17; from H-7' to C-1', respectively, were observed and established its 2D planar structure as shown (Figure 1). The NOESY analysis (Figure 1) constructed the stereochemical configurations of **1** as the same as those of trichilin E, and full assignments of all the proton and carbon signals were completed with the assistance of all 2D experiments. Conclusively, the chemical structure of **1** was established and named trivially as trichilin G (Figure 1) followed the previous convention [11].

In addition, seven known compounds were identified as meliatoxin B1 (**2**) [12], meliasenin S (**3**) [13], eichlerianic acid (**4**) [14], apigenin (**5**) [15], quercetin 3-*O*-[α -L-rhamnopyranosyl-(1→6)]- β -D-glucopyranoside (rutin) (**6**) [16], scopoletin (**7**) [17,18], vanillic acid (**8**) [19], taraxerol (**9**) [20], β -

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sitosterol (**10**) [21], and β -sitosterol-3-O- β -D-glucopyranoside (**11**) [22,23], respectively, based on the comparison of their spectroscopic and spectrometric profiles. Moreover, a cellular model in isolated human neutrophils was used to evaluate the anti-inflammatory potential of the new compound **1** from *M. azedarach* for its inhibitory effects on superoxide anion generation and elastase release by human neutrophils in response to formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (fMLP/CB) [7,8]. However, trichilin G (**1**) did not display any significant inhibitions of fMLP/CB induced superoxide anion generation at 10 μ M.

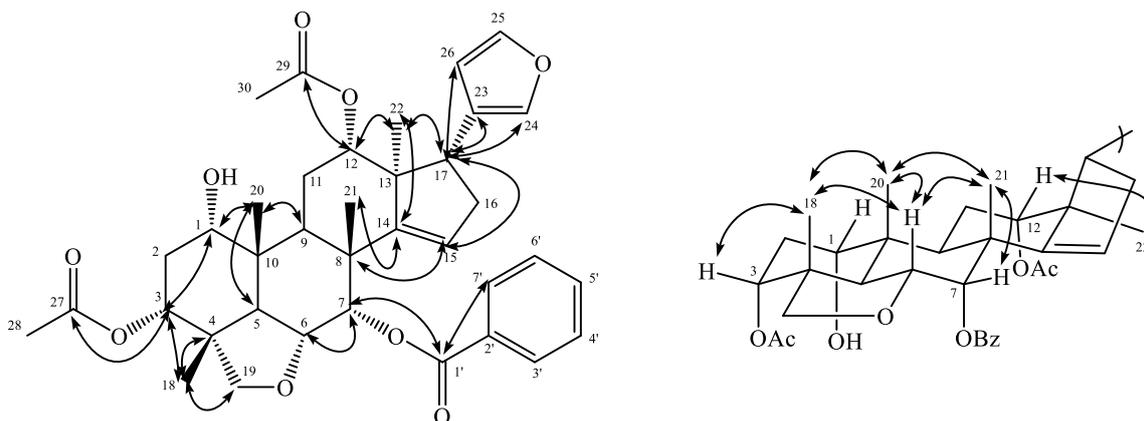


Figure 1. Structure and significant HMBC (\rightarrow) and NOESY (\leftrightarrow) correlations of compound **1**

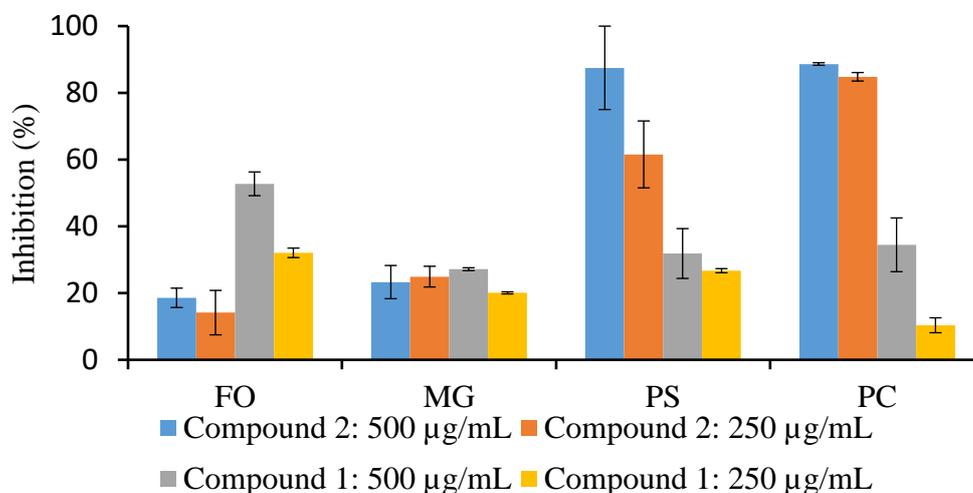


Figure 2. The inhibitory effects of compounds **1** and **2** on the mycelial growth of four phytopathogenic fungi* *Fusarium oxysporum* (FO), *Magnaporthe grisea* (MG), *Phytophthora* spp. (PS), and *P. capsici* (PC)

*The fungi were incubated at 25–28 $^{\circ}$ C and the mycelial growth of each fungus was measured 2–7 days after incubation..

A most interesting group of bioactive and structurally unique triterpenoids are the limonoids, which are commonly found to occur in *Melia* and *Citrus* plant species. The well-known bioactivities of the Meliaceae limonoids are insecticidal and antifeeding activities against pest insects. The insecticidal limonoids such as azadirachtin, nimbin, salannin and the extracts of those limonoids have been used as active ingredients in many commercial pesticides in controlling agriculture [1-3]. However, there are a few reports of antifungal activity of the Meliaceae limonoids against phytopathogenic fungi. In a

previous study by Carpinella *et al.* (2003), the organic solvent extracts derived from the fruits and leaves of *M. azedarach* were found to have the antifungal effects on phytopathogenic fungi *Aspergillus flavus*, *Diaporthe phaseolorum* var. *meridionales*, *F. oxysporum*, *F. solani*, *F. verticillioides*, and *Sclerotinia sclerotiorum*. The active principles in the extracts of *M. azedarach* were determined to be non-limonoids vanillin, 4-hydroxy-3-methoxycinnamaldehyde, and (\pm)-pinoresinol with MIC values ranging from 600 to 1000 $\mu\text{g/mL}$ [24]. In our study, among the test phytopathogenic fungi, oomycete *Phytophthora* spp. and *P. capsici* were the most sensitive to compounds **1** and **2** (Fig. 2). While the mycelial growths of *Fusarium oxysporum* and *Magnaporthe grisea* were moderately affected in the treatment with **1** and **2**. Compound **1** exerted weak to moderate antifungal activity against the four test fungi; at 500 $\mu\text{g/mL}$, it inhibited 52.8, 27.2, 31.9 and 34.5% of the mycelial growth of *F. oxysporum*, *M. grisea*, *Phytophthora* spp., and *P. capsici*, respectively. The calculated IC_{50} values of compound **2** were determined to be 103.8 (CI: 82.6-130.5) $\mu\text{g/mL}$ for PS and below 62.5 $\mu\text{g/mL}$ for PC, respectively. Compound **2** showed the best antifungal activity against both PS and PC in a dose-dependent manner (Fig. 3).

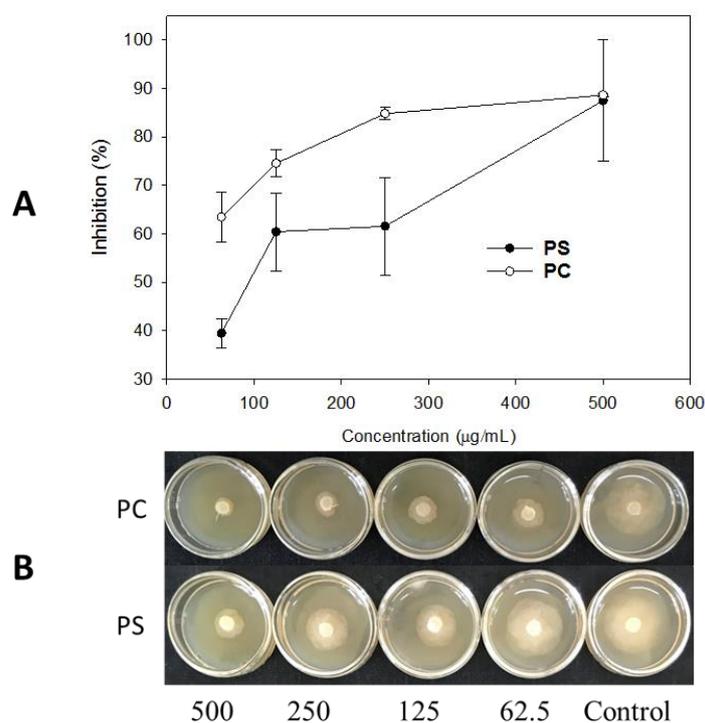


Figure 3. The antifungal activity of compound **2** against *Phytophthora* spp. (PS) and *P. capsici* (PC) in a dose-dependent manner (A). The petri dishes were treated with **2** at concentrations ranging from 62.5 to 500 $\mu\text{g/mL}$ (B)

Meliatoxin B1, a trichilin-class limonoid possessing C-15 keto structure, was previously isolated from the fruits of *M. azedarach* and *M. toosendan* and showed considerable cytotoxicity against tumor cell lines P388 (IC_{50} 5.4 $\mu\text{g/mL}$) and KB (IC_{50} >10 $\mu\text{g/mL}$) [25, 26]. However, the antimicrobial activity of compound **2** has not been reported up to date. Concerning the antimicrobial activity of tirucallane-type triterpenoids such as meliasenin S, human pathogenic bacteria *Pseudomonas aeruginosa* and *Escherichia coli* were inhibited at MIC values of 64 and 128 $\mu\text{g/mL}$, respectively, when treated with meliasenin G isolated from *Walsura trichostemon* roots [27].

With a structural characterization similar to trichilin G (**1**), trichilin B and 1-cinnamoyltrichilin isolated from the fruits of *M. azedarach* were observed to suppress the viability of HL-60 human leukemia cells by activating the p38 pathway and inducing apoptosis [28]. In a previous investigation of the cytotoxic constituents of *M. azedarach*, trichilin M and ohchinin benzoate were also found as active against PANC1 cells with IC_{50} values of 27.06 μM and 21.17 μM , respectively [29].

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To the best of our knowledge, many studies demonstrated the insecticidal and antifeedant activity, and cytotoxicity of limonoids from *M. azedarach*; however, this is the first report of the antifungal activity of compounds **1** and **2** against phytopathogenic fungi. Our antifungal bioassay results indicated that the limonoids from *M. azedarach* could be a promising resource to search active ingredients for fungicides in further researches.

4. Conclusion

In this work, eleven chemical constituents, including one new triterpenoid trichilinin G (**1**), were identified from the fruit extract of *M. azedarach*. The structure of **1** was established by various spectroscopic and mass spectrometric analyses. Compounds **1** and **2** exhibited the *in vitro* antifungal activity against various fungi *F. oxysporum*, *M. grisea*, *Phytophthora* spp., and *P. capsici*. Notably, meliatoxin B1 (**2**) was the best inhibitor against oomycete species *Phytophthora* spp., and *P. capsici*. In addition, the inhibitory effects of **1** on superoxide anion generation and elastase release by human neutrophils were assessed in a cellular model, but no significant effects were observed.

Acknowledgments

This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.01-2018.315.

Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/records-of-natural-products>

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