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Research Article

FOUR COMPOUNDS FROM *DICRANOPTERIS LINEARIS* SPORES

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ABSTRACT

*Dicranopteris linearis, a widely utilized plant species in traditional Vietnamese medicine, has been chemically investigated. Four compounds (**1**–**4**), including syringaresinol (**1**), shikimic acid (**2**), angelicin (**3**), and 3,4-dihydroxycinnamic acid (**4**) were isolated and structurally elucidated. Extensive spectroscopic methods were employed for structural elucidation. These isolates were subsequently evaluated for their alpha-glucosidase inhibitory activity and inhibitory effect on nitric oxide production in LPS-stimulated RAW 264.7 cells. Isolated compounds exhibited no inhibitory activity in either alpha-glucosidase or nitric oxide inhibition assays.*

Keywords: alpha-glucosidase; angelicin; *Dicranopteris linearis;* nitric oxide inhibition; shikimic acid; syringaresinol

1. Introduction

Comprehensive reviews have underscored ferns as widely recognized sources with numerous traditional applications. These include hepatoprotective effects, antihyperglycemic properties, leishmanicidal activity, and trypanocidal activity (Cao et al., 2017; Kumar et al., 2010). *Dicranopteris linearis* (Burm. F.) Underw. is a globally distributed fern species that has been traditionally utilized in East Asian countries for the treatment of diverse diseases. In Malaysia, it is employed to alleviate fevers, while in Indochina, it is utilized to combat intestinal worms (Kamisan et al., 2014). In India, it is used to treat infertility in women, and in Papua New Guinea, it is utilized for wound healing (Sarker & Hossain, 1970). Various pharmacological properties of *D. linearis* have been reported, including anticancer, antibacterial, antioxidant, analgesic, and anti-HIV activities (Chen et al., 2014; Li et al., 2008; Ponnusamy et al., 2015; Zakaria et al., 2021). A comprehensive chemical analysis of *D. linearis* was conducted, revealing the presence of over 50 compounds, predominantly found in the leaves of the plant (Chen et al., 2014; Duong et al., 2023, 2024; Li et al., 2008; Ponnusamy et al., 2015; Raja et al., 1995). Numerous pharmaceutical properties of extracts of *D. linearis* leaves have been the subject of scientific

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investigation. Our previous report indicated that the organs of *D. linearis* may possess potent alpha-glucosidase inhibitors (Duong et al., 2023). Recently, *D. linearis* spores have been chemically investigated using a bioactive-guide procedure based on antioxidant activity, including DPPH and ABTS (Duong et al., 2024). This study aims to elucidate the chemical composition and bioactive properties of the spores of *D. linearis*, with a particular emphasis on their alpha-glucosidase and nitric oxide inhibitory activities.

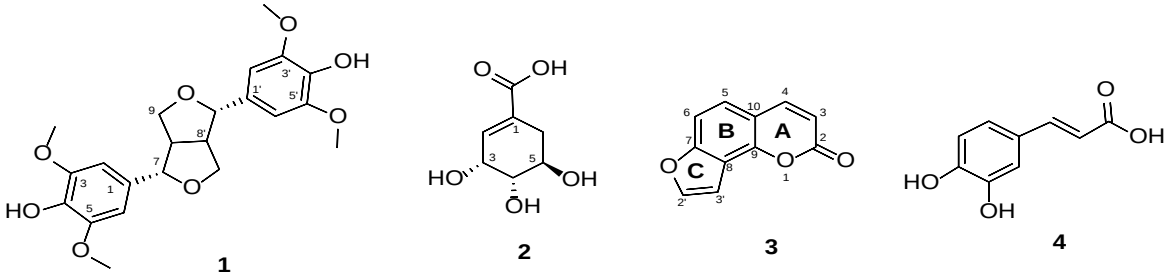

Figure 1. *Chemical structures of* ***1-4***

2. Experiments

2.1. General experimental procedures

The NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz for ^{1}H–NMR and 125 MHz for ^{13}C–NMR) in acetone-d_6 and $CDCl_3$. Thin-layer chromatography was carried out on silica gel 60 (Merck, 40-63 μm), and spots were visualized by spraying with 10% H_2SO_4 solution, followed by heating.

2.2. Plant materials

In November 2022, spores of *Dicranopteris linearis* were collected in Binh Thuan Province, Vietnam and were authenticated by Assoc. Prof. Van-Son Dang, Institute of Tropical Biology, Vietnam Academy of Science and Technology (VAST). A voucher specimen (No. UE-P017A) was deposited in the VNM Herbarium, Institute of Tropical Biology, VAST.

2.3. Extraction and isolation

The dried powder of *D. linearis* spores (200 g) was extracted with methanol (10 x 1 L, each 8 hours) at room temperature using the maceration method. After removing the solvents using an evaporator, a crude methanol extract (12 g) was obtained. This extract was separated by silica gel column chromatography (CC) using the gradient system of *n*-hexane-ethyl acetate (1:3-0:1, *v*/*v*) followed by methanol to afford five fractions EA1-EA5. Fraction EA4 (3.6 g) underwent further purification using silica gel CC, resulting in four subfractions (EA4.1-EA4.4). Fraction EA4.1 (850 mg) was applied to silica gel CC, isocratically eluted with EtOAc-MeOH-H_2O (100:0:0 then 98:2:0.1, v/v/v) to obtain three fractions T1-T3. Fraction T1 (67 mg) was further purified using silica gel CC, eluted with EtOAc-MeOH-H_2O (100:0:0 then 95:5:0.1, v/v/v) to yield three compounds **1** (4.0 mg), **3** (3.5 mg), and **4** (21.0 mg). Fraction T3 (255 mg) underwent further purification using silica gel CC, resulting in compound **2** (11.5 mg).

Syringaresinol (**1**). Colorless oil; ^{1}H NMR (acetone-d_6, 500 MHz): δ_H 6.70 (2H, s, H-2/2′ and H-6/6′), 4.68 (2H, d, J = 4.5 Hz, H-7/7′), 3.11 (2H, m, H-8/8′), 4.30 (2H, m, H-9a/9′a),

3.90 (2H, dd, *J* = 3.5, 1.0 Hz, H-9b/9′b), 3.84 (12H, s, 4 x OCH_3). ^{13}C NMR (acetone-d_6, 125 MHz): 133.1 (C-1/1′), 103.4 (C-2/2′ and C-6/6′), 147.6 (C-3/3′ and C-5/5′), 136.9 (C-4/4′), 85.8 (C-7/7′), 54.0 (C-8/8′), 71.7 (C-9/9′), 56.5 (4 x OCH_3).

Shikimic acid (**2**). White amorphous powder; ^{1}H NMR (methanol-d_4, 500 MHz): δ_H 6.77 (1H, brs, H-2), 4.02 (1H, dd, *J* = 8.5, 5.5 Hz, H-3), 3.70 (1H, dd, *J* = 7.3, 4.3 Hz, H-4), 4.40 (1H, m, H-5), 2.69 (1H, dd, *J* = 18.0, 5.5 Hz, H-6a), 2.17 (1H, dd, *J* = 18.0, 4.5 Hz, H-6b). ^{13}C NMR (methanol-d_4, 125 MHz): 171.1 (C=O), 136.8 (C-1), 130.8 (C-2), 66.1 (C-3), 71.5 (C-4), 66.9 (C-5), 30.9 (C-6).

Angelicin (**3**). White amorphous powder; ^{1}H NMR (acetone-d_6, 500 MHz): δ_H 6.39 (1H, d, *J* = 9.5 Hz, H-3), 8.10 (1H, d, *J* = 9.5 Hz, H-4), 7.55 (1H, d, *J* = 8.5 Hz, H-5), 7.63 (1H, d, *J* = 8.5 Hz, H-6), 7.55 (1H, d, *J* = 8.5 Hz, H-5), 8.01 (1H, d, *J* = 2.0 Hz, H-2′), 7.21 (1H, d, *J* = 2.0 Hz, H-3′). ^{13}C NMR (acetone-d_6, 125 MHz): 171.1 (C=O), 136.8 (C-1), 130.8 (C-2), 66.1 (C-3), 71.5 (C-4), 66.9 (C-5), 30.9 (C-6). 160.8 (C-2), 114.9 (C-3), 145.6 (C-4), 125.4 (C-5), 109.3 (C-6), 158.4 (C-7), 117.4 (C-8), 150.0 (C-9), 114.9 (C-10), 147.6 (C-2′), 104.5 (C-3′).

3,4-Dihydroxycinnamic acid (**4**). White amorphous powder. ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data were consistent with those reported previously (Oboh et al., 2015).

2.4. Alpha-Glucosidase Inhibition and Nitric oxide inhibition Assays

The alpha-glucosidase inhibitory activity of compounds **1**-**4** was determined using a method adapted from previously published protocol (Duong et al., 2024). The samples were analyzed in triplicate at ten distinct concentrations ranging from the IC_{50} values, and the mean values were recorded. NO inhibition of compounds **1**-**4** were determined using the same procedure previously reported.(Ngoc Mai et al., 2024; Sukandar et al., 2023) L-NMMA was used as a positive control. Each sample was analyzed in triplicate at five different concentrations around the IC_{50} values, and the mean values were recorded.

3. Results and discussion

Compound **1** was obtained as colorless oil. The ^{1}H-NMR spectrum of **1** showed the presence of a symmetric benzene ring characterized by four aromatic proton signals at δ_H 6.70 (4H, s, H-2/H-6 and H-2′/H-6′). In addition, the ^{1}H-NMR spectrum showed the signals of two oxymethine protons at δ_H 4.68 (2H, d, *J* = 4.5 Hz, H-7/H-7′), two methine protons at δ_H 3.11 (2H, m, H-8/H-8′), four oxymethylene protons at δ_H 4.30 (2H, m, H-9), 3.90 (2H, dd, *J* = 3.5, 1.0 Hz, H-9′) and four methoxy groups at δ_H 3.84 (12H, s). These findings indicated that **1** is a symmetric lignan. The ^{13}C-NMR spectral data of **1** showed the presence of 12 aromatic methine carbons at δ_C 133.1 (C-1/C-1′), 103.4 (C-2/C-2′), 147.6 (C-3/C-3′ and C-5/C-5′), 136.9 (C-4/C-4′), 103.5 (C-6/C-6′); 2 oxymethine carbon at δ_C 85.8 (C-7/C-7′); 2 carbon methine at δ_C 54.0 (C-8/C-8′); 2 methylene groups at δ_C 71.8 (C-9/C-9′) and 4 methoxy groups at δ_C 56.5. Comparison of the NMR data of **1** and those of syringaresinol showed the high similarity, thus suggesting that the structure of **1** is syringaresinol (Ban et al., 2020).

Compound **2** was obtained as a white amorphous powder. The ^{1}H-NMR (500 MHz, methanol-d_4) spectrum of **2** showed the presence of an olefinic methine at δ_H 6.77 (1H, brs, H-

2), three oxymethines at δ_H 4.02 (1H, dd, J = 12.0, 5.5 Hz, H-3), 3.70 (1H, dd, J = 7.3, 4.3, H-4), and 4.40 (1H, m, H-5), a methylene group at δ_H 2.17 (1H, dd, J = 18.0, 5.5 Hz, H-6) and 2.69 (1H, dd, J = 18.0, 4.5 Hz, H-6). The ^{13}C-NMR (125 MHz, methanol-d_4) spectrum of **2** showed the presence of seven carbon signals including: a carboxyl carbon at δ_C 168.7, a substituted olefinic carbon at δ_C 138.6 (C-1), an olefinic methine carbon at δ_C 130.1 (C-2), three oxymethine carbons at δ_C 130.1 (C-3), 66.7 (C-4), 72.3 (C-5), and a methylene carbon at δ_C 31.4 (C-6). Comparison of the NMR data of **2** and those of shikimic acid showed the high similarity, thus suggesting that the structure of **2** is shikimic acid (Bochkov et al., 2011).

Compound **3** was obtained as a white amorphous powder. The ^{1}H NMR spectrum showed the presence of two aromatic protons [δ_H 7.55 (1H, d, J = 8.5 Hz, H-5) and δ_H 7.63 (1H, d, J = 8.5 Hz, H-6)], four olefinic protons [δ_H 6.39 (1H, d, J = 9.5 Hz, H-3), 8.10 (1H, d, J = 9.5 Hz, H-4), 8.01 (1H, d, J = 2.0 Hz, H-2′), 7.21 (1H, d, J = 2.0 Hz, H-3′)]. The ^{13}C NMR data in accordance with HSQC spectrum exhibited 11 carbon signals: a carbonyl carbon at δ_C 160.8 (C-2); four substituted olefinic carbons at δ_C 158.4 (C-7), 117.4 (C-8), 150.0 (C-9), and 114.9 (C-10); two aromatic methine carbons at δ_C 125.4 (C-5), and 109.3 (C-6), four olefinic methine carbons at δ_C 114.9 (C-3), 145.6 (C-4), 147.6 (C-2′), and 104.5 (C-3′). HMBC correlations of proton H-3 to C-4 (δ_C 145.6), of H-4 to C-2 (δ_C 160.8), of proton H-5 to C-10 (δ_C 114.9) supported the structure of the A-ring. In addition, HMBC correlations of protons H-6 and H-2′ to carbons C-9 (δ_C 150.0) and C-7 (δ_C 158.4) and of proton H-3′ to C-7 (δ_C 158.4) indicated the connection between the B-ring and C-ring. A comparative analysis of the NMR data of **3** and those of angelicin revealed a striking degree of similarity, strongly suggesting that the structure of **3** is identical to that of angelicin (Mar et al., 2001).

To the best of our knowledge, compounds **1-3** were initially identified in the plant. Compounds **1-4** were evaluated for their alpha-glucosidase inhibitory activity and inhibitory effect on nitric oxide production in LPS-stimulated RAW 264.7 cells. Isolated compounds exhibited no inhibitory activity in either alpha-glucosidase or nitric oxide inhibition assays. None of the compounds exhibited any activity.

4. Conclusions

From *Dicranopteris linearis* spores, four compounds, syringaresinol (**1**), shikimic acid (**2**), angelicin (**3**), and 3,4-dihydroxycinnamic acid (**4**), were isolated from the MeOH extract of *Dicranopteris linearis*. To the best of our knowledge, compounds **1-3** were first reported in the plant *Dicranopteris linearis*. Further studies on this species are in progress.

❖ ***Conflict of Interest:*** *Authors have no conflict of interest to declare.*

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BỐN HỢP CHẤT TỪ HẠT RÁNG TÂY SƠN *DICRANOPTERIS LINEARIS*

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TÓM TẮT

*Dicranopteris linearis, một loài thực vật được sử dụng rộng rãi trong y học cổ truyền Việt Nam, đã được thực hiện nghiên cứu về mặt hóa học. Bốn hợp chất syringaresinol (**1**), shikimic acid (**2**), angelicin (**3**) và 3,4-dihydroxycinnamic acid (**4**) đã được phân lập và được xác định cấu trúc hóa học. Các phương pháp phổ NMR kết hợp với so sánh với dữ liệu đã công bố đã được sử dụng để xác định cấu trúc hóa học của các hợp chất. Các hợp chất này đã được đánh giá về hoạt tính ức chế alpha-glucosidase và tác dụng ức chế đối với việc sản xuất nitric oxide trong tế bào RAW 264.7 được kích thích LPS. Tuy nhiên, các hợp chất không thể hiện hoạt tính ức chế đối với alpha-glucosidase hoặc nitric oxide.*

Từ khóa: alpha-glucosidase; angelicin; *Dicranopteris linearis;* nitric oxide inhibition; shikimic acid; syringaresinol