HPU2 Journal of Sciences:
Natural Sciences and Technology

journal homepage: https://sj.hpu2.edu.vn

Article type: Review article

Chemical Constituents from the Whole Plant of *Scutellaria indica*

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Abstract

Three compounds, naringenin (**1**), arctiin (**2**) and martinoside (**3**) were isolated from the whole plant of *Scutellaria indica* (Labiatae). The chemical structures of these compounds were determined by spectroscopic analyses including 1D- and 2D-NMR. Compounds **2** and **3** were isolated from *S. indica* for the first time.
Keywords: Scutellaria indica, Labiatae, Flavonoid, Lignan;

1. Introduction

Scutellaria indica (Labiatae) is a small herb, 15–30 cm tall, with erect stems arising from a prostrate base [1]. The whole herb of *S. indica* is used to treat hemoptysis, hematemesis, cancer, and other diseases in China. It is distributed widely in Korea, China, Taiwan, Japan, and Southeast Asia [2]. Several secondary metabolites were isolated from this plant such as flavonoids and phenylpropanoids, which demonstrated the effects on cancer [3] and inflammation [4,5]. The methanolic extract of the roots of *S. indica* showed potently cytotoxic activity against L1210 and HL60 cells in an earlier *in vitro* screening test.[3] Kim *et al.* reported that compounds isolated from the ethyl acetate fraction of *S. indica* inhibited arginase II activity [4]. Also, Cuong *et al.* reported that flavonoids isolated from the ethyl acetate fraction of *S. indica* inhibited nitric oxide production [5]. However, the chemical composition of this plant was not still examined thoroughly. In this paper, we describe the isolation and structural determination of three compounds (**1**–**3**) from the ethyl acetate fraction of the methanol extract of *S. indica.*

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https://doi.org/10.56764/hpu2.jos.2022.1.2.44-51

Received date: 26-12-2022 ; Revised date: 26-12-2022 ; Accepted date: 28-12-2022

2. Materials and methods

2.1. General experimental procedure

Optical rotation was measured with a JASCO DIP 370 digital polarimeter. UV spectra were obtained in MeOH using a Thermo 9423AQA2200E UV spectrometer, and IR spectra were obtained on a Bruker Equinox 55 FT-IR spectrometer. The nuclear magnetic resonance (NMR) spectra were obtained on Varian Unity Inova 400 MHz spectrometer. Silica gel (Merck, 63–200 μm particle size) and RP-18 silica gel (Merck, 75 μm particle size) were used for column chromatography. TLC was carried out using Merck silica gel 60 F_{254} and RP-18 F_{254} plates. HPLC was performed using a Waters 600 Controller system with a UV detector and a YMC Pak ODS-A column (20 × 250 mm, 5 μm particle size, YMC Co., Ltd., Japan) and HPLC solvents were from Burdick & Jackson, USA.

2.2. Plant material

S. indica was collected in Lam Dong province, Vietnam, in May 2019. The sample was identified by Dr. Nguyen Quoc Binh (Vietnam National Museum of Nature, Vietnam Academy of Science and Technology). A voucher specimen, HC-BMT-05, is deposited at Faculty of Natural Science and Technology, Tay Nguyen University, Buon Ma Thuot city, Dak Lak province, Vietnam

2.3. Extraction and isolation

The air-dried whole plant of *S. indica* (2.2 kg) was extracted with MeOH (10 L) at room temperature for seven days and then MeOH extract (385 g) was suspended in hot-water (1.5 L) and partitioned with *n*-hexane (3 L x 3), ethyl acetate (3 L x 3), and *n*-butanol (3 L × 3), successively. The resulting fractions were concentrated *in vacuo* to give the hexane- (145 g), EtOAc- (52.0 g) and BuOH-soluble fraction (16.8 g), respectively.

The EtOAc-soluble fraction (52.0 g) was applied to a silica gel column eluted with $CHCl_3$–MeOH (50:1 to 0:1) to yielded 15 subfractions (E1 ~ E15). Subfraction E.9 (1.65 g) was applied to a reverse phase silica gel column and eluted with MeOH–H_2O (1:1 to 5:1) to afford three subfractions (E9.1 ~ E9.3). Compound 1 (5.3 mg) and compound 2 (12.4.0 mg) were isolated from subfraction E9.2 by using HPLC on a RP-18 column using MeOH- H_2O (70 : 30 → 90 : 10). Subfractions E14 (2.22 g) was subjected on a silica gel column, eluted with $CHCl_3$–MeOH (10:1 to 1:1) to afford nine subfractions (E14.1 ~ E14.9). Subfraction E.14.8 (110 mg) was further subjected to HPLC on a RP-18 column using MeOH- H_2O (25 : 75 → 50 : 50) to obtain compound 3 (50.8 mg), respectively.

Naringenin (1): light brown powder; ESI-MS *m/z*: 273.1 $[M + H]^+$ (calcd. for $C_{15}H_{13}O_5$); ^{1}H-NMR (400 MHz, methanol-d_4) δ_H (ppm): 5.35 (1H, dd, J = 3.2, 12.0 Hz, H-2), 2.71 (1H, dd, J = 3.2, 13.2 Hz, H-3$_{eq}$), 3.00 (1H, dd, J = 12.0, 13.2 Hz, H-3$_{ax}$), 5.91 (2H, d, J = 1.6 Hz, H-6/H-8), 7.32 (2H, d, J = 8.0 Hz, H-2′/H-6′), 6.84 (2H, d, J = 8.0 Hz, H-3′/H-5′); ^{13}C-NMR (75 MHz, methanol-d_4) δ_C (ppm): 80.6 (C-2), 42.1 (C-3), 197.9 (C-4), 165.0 (C-5), 96.3 (C-6), 168.4 (C-7), 97.2 (C-8), 165.6 (C-9), 103.5 (C-10), 131.2 (C-1′), 129.1 (C-2′/C-6′), 116.4 (C-3′/C-5′), 159.1 (C-4′).

Arctiin (2): light brown gum; ESI-MS *m/z*: 535.2 $[M + H]^+$ (calcd. for $C_{27}H_{35}O_{11}$); ^{1}H-NMR (400 MHz, methanol-d_4) δ_H (ppm): 6.57 (1H, s, H-2), 6.72 (1H, d, J = 8.0 Hz, H-5), 6.58 (1H, d, J = 8.0 Hz, H-6), 2.90 (1H, m, H-7a), 2.81 (1H, m, H-7b), 2.67 (1H, m, H-8), 6.82 (1H, d, J = 1.2 Hz, H-2′), 7.07 (1H, d, J = 8.4 Hz, H-5′), 6.64 (1H, dd, J = 1.2, 8.4 Hz, H-6′), 2.53 (2H, m, H-7′), 2.46 (1H, m, H-8′), 4.17 (1H, dd, J = 7.2, 10.0 Hz, H-9′a), 3.92 (1H, dd, J = 4.4, 10.0 Hz, H-9′b), 4.88 (1H, d, J = 8.0 Hz, H-1″), 3.47 (1H, m, H-2″), 3.45 (1H, m, H-3″), 3.37 (1H, m, H-4″), 3.34 (1H, H-5″), 3.84 (1H, dd, J = 7.2, 10.0 Hz, H-6″a), 3.64 (1H, dd, J = 4.4, 10.0 Hz, H-6″b), 3.72 (3H, s, 3-OCH_3), 3.70 (6H, s,

3′,4′-OCH_3); ^{13}C-NMR (75 MHz, methanol-d_4) δ_C (ppm): 132.7 (C-1), 113.6 (C-2), 150.6 (C-3), 149.2 (C-4), 113.8 (C-5), 122.1 (C-6), 35.4 (C-7), 47.6 (C-8), 181.3 (C-9), 133.3 (C-1′), 114.8 (C-2′), 150.5 (C-3′), 146.8 (C-4′), 117.9 (C-5′), 123.0 (C-6′), 38.9 (C-7′), 42.5 (C-8′), 72.9 (C-9′), 102.9 (C-1′′), 74.9 (C-2′′), 77.8 (C-3′′), 71.3 (C-4′′), 78.1 (C-5′′), 62.5 (C-6′′), 56.8 (C-3), 56.6 (C-3′), 56.5 (C-4′).

Martinoside (3): brown solid; FAB-MS *m/z*: 653.2 $[M + H]^+$ (calcd. for $C_{31}H_{41}O_{15}$); ^{1}H-NMR (400 MHz, methanol-d_4) δ_H (ppm): 6.76 (1H, d, *J* = 2.0 Hz, H-2), 6.82 (1H, d, *J* = 8.4 Hz, H-5), 6.69 (1H, dd, *J* = 2.0, 8.4 Hz, H-6), 2.83 (1H, t, 6.8 Hz, H-7), 4.07 (1H, m, H-8a), 3.75 (1H, m, H-8b), 4.39 (1H, d, J = 7.6 Hz, H-1′), 3.95 (1H, m, H-2′), 3.85 (1H, m, H-3′), 4.94 (1H, m, H-4′), 3.42 (1H, m, H-5′), 3.65 (1H, m, H-6′a), 3.54 (1H, m, H-6′b), 5.32 (1H, d, *J* = 1.2 Hz, H-1′′), 3.53 (1H, m, H-2′′), 3.61 (1H, m, H-3′′), 3.32 (1H, m, H-4′′), 3.62 (1H, m, H-5′′), 1.12 (3H, d, *J* = 6.4 Hz, CH_3-6′′), 7.20 (1H, d, *J* = 2.0 Hz, H-2′′′), 6.83 (1H, d, *J* = 8.4 Hz, H-5′′′), 7.09 (1H, dd, *J* = 2.0, 8.4 Hz, H-6′′′), 7.67 (1H, d, *J* = 16.0 Hz, H-7′′′), 6.49 (1H, d, *J* = 16.0 Hz, H-8′′′), 3.81 (3H, s, 4-OCH_3), 3.89 (3H, s, 4′′′-OCH_3); ^{13}C-NMR (75 MHz, methanol-d_4) δ_C (ppm): 132.9 (C-1), 117.1 (C-2), 147.4 (C-3), 147.6 (C-4), 112.9 (C-5), 121.8 (C-6), 36.6 (C-7), 72.4 (C-8), 104.2 (C-1′), 72.2 (C-2′), 81.6 (C-3′), 70.7 (C-4′), 76.2 (C-5′), 62.4 (C-6′), 103.0 (C-1′′), 76.0 (C-2′′), 70.5 (C-3′′), 73.8 (C-4′′), 72.1 (C-5′′), 18.5 (6′′-CH_3), 127.7 (C-1′′′), 111.9 (C-2′′′), 149.4 (C-3′′′), 150.8 (C-4′′′), 116.6 (C-5′′′), 124.4 (C-6′′′), 148.0 (C-7′′′), 115.2 (C-8′′′), 168.3 (C-9′′′), 56.6 (4-OCH_3), 56.5 (4′′′-OCH_3).

3. Results and discussion

The methanol extract of the whole plant of *S. indica* was partitioned into hexane, ethyl acetate and butanol-soluble fractions and a water layer. Chromatographic purification of the ethyl acetate-soluble fraction led to the isolation of three compounds (**1**–**3**) (Figure 1).

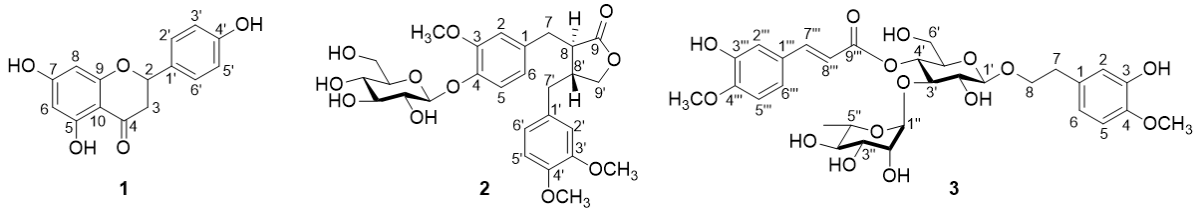

Figure 1. Chemical structure of isolated compounds **1**–**3** from S. indica

Compound **1** was obtained as a light brown powder. A methylene carbon at δ_C 42.1 (C-3), an oxymethine carbon at δ_C 80.6 (C-2), and a carbonyl carbon at δ_C 197.9 in the ^{13}C-NMR spectrum indicated **1** to be a flavanone [6]. The ^{1}H NMR spectrum of **1** revealed the presence of an oxymethine proton at δ_H 5.35 (1H, dd, *J* = 3.2, 12.0 Hz, H-2), and a methylene group at δ_H 2.71 (1H, dd, *J* = 3.2, 13.2 Hz, H-3$_{eq}$), 3.00 (1H, dd, *J* = 12.0, 13.2 Hz, H-3$_{ax}$). The signals of two aromatic protons at δ_H 5.91 (2H, d, *J* = 1.6 Hz, H-6/H-8) and a 1,4- disubstituted benzene ring characterized with an A_2B_2 spin system [δ_H 7.32 (2H, d, *J* = 8.0 Hz, H-2′/H-6′), 6.84 (2H, d, *J* = 8.0 Hz, H-3′/H-5′)] (Figure 1). The ^{13}C-NMR spectrum exhibited fifteen signals due to twelve sp^2 carbons [δ_C 165.0 (C-5), 96.3 (C-6), 168.4 (C-7), 97.2 (C-8), 165.6 (C-9), 103.5 (C-10), 131.2 (C-1′), 129.1 (C-2′/C-6′), 116.4 (C-3′/C-5′), 159.1 (C-4′).at δ_C 96.3–168.4], indicating the presence of two benzene rings (Figure 1). The molecular formula of **1** was $C_{15}H_{12}O_5$ from the molecular ion peak at *m/z* 273.1 for the $[M + H]^+$ ion in the ESI-MS. Based on these evidences and in comparison with the published data compound **1** was identified

as naringenin [7]. This compound was found in some edible fruits, like Citrus species and tomatoes [8-10], and figs belonging to smyrna-type Ficus carica [11]. Naringenin was found to show anti-atherogenic and anti-inflammatory effects [12] and prevents fatty liver [13].

Compound **2** was obtained as a light brown gum with a molecular formula $C_{17}H_{34}O_{11}$, as determined by ESI-MS at *m/z* 535.2 for the $[M + H]^+$ ion. The ^{1}H-NMR spectrum displayed signals for two methine protons [(δ_H 2.67 (1H, m, H-8) and 2.46 (1H, m, H-8′)], oxygenated methylene [δ_H 4.17 (1H, dd, *J* = 7.2, 10.0 Hz, H-9′a), 3.92 (1H, dd, *J* = 4.4, 10.0 Hz, H-9′b)], two sets of ABX-spin systems of the phenyl protons from δ_H 6.57 ppm to δ_H 7.05 ppm, two benzylic protons [δ_H 2.90 (1H, m, H-7a), 2.81 (1H, m, H-7b)], and the other two benzylic protons at δ_H 2.53 (2H, m, H-7′) (Figure 1). The ^{13}C-NMR spectrum showed signals for a carbonyl carbon, three sp^3 methylenes, one sp^3 methine, six sp^2 quaternary carbons, one sp^3 quaternary carbon, and six aromatic protons. This indicated a dibenzylbutyrolactone lignan with a structure similar to (+)-nortrachelogenin isolated from *Wikstroemia indica* [14]. Furthermore, the ^{1}H-NMR spectrum showed three methoxy groups at δ_C 3.72 (3H, s, 3-OCH_3), 3.70 (6H, s, 3′,4′-OCH_3), which correlated with the quaternary carbons at δ_C 150.6 (C-3), 150.5 (C-3′) and 146.8 (C-4′), respectively (Figure 1). These signals led to the identification of the positions of the two methoxy groups. In addition, the ^{1}H-NMR spectrum of **2** showed an anomeric proton at δ_H 4.88 (1H, d, *J* = 8.0 Hz, H-1″) and six oxygenated protons [δ_H 3.47 (1H, m, H-2″), 3.45 (1H, m, H-3″), 3.37 (1H, m, H-4″), 3.34 (1H, H-5″), 3.84 (1H, dd, *J* = 7.2, 10.0 Hz, H-6″a), 3.64 (1H, dd, *J* = 4.4, 10.0 Hz, H-6″b)], suggesting the appearance of one sugar unit (Figure 1). The sugar was assigned as glucopyranoside on the basis of NMR data and the R*f* value compared with authentic glucose after acid hydrolysis of **2**. The absolute configuration and linkage of glucose were determined as D using gas chromatography and β on the basis of the $J_{1,2}$ value (8.0 Hz) of the anomeric proton. Thus, on the basis of the above evidence, compound **2** was identified as arctiin when compared with literature data [15]. This compound was isolated from *S. indica* for the first time. Arctiin detected in many plants of the Asteraceae family, particularly the greater burdock (*Arctiumlappa*) and *Centaureaimperialis*, and in *Trachelospermumasiaticum*, *Saussureaheteromalla* [16], and *Forsythia viridissima* [17]. This contains many kinds of bioactivities, such as: anti-inflammatory [18], antiproliferative and cytotoxicity [19, 20], antioxidative [21, 22], antitumor [23-25], toxicity [26-28], antidiabetic [29,30], antiadipogenic [31], antibacterial [32], UVB protective effect [33,34], Influenza therapeutic agent [35] …

Compound **3** was isolated as brown solid with the molecular formula $C_{31}H_{40}O_{15}$, as determined by the FAB-MS at *m/z* 653.2 $[M + H]^+$. The ^{1}H-NMR spectrum of **3** showed signals of two aromatic rings, both with coupling patterns corresponding to 1,3,4-trisubstituted benzene: δ_H 6.69 (H-6), 6.82 (H-5), and 6.76 (H-2) and δ_H 6.83 (H-5‴), 7.09 (H-6‴) and 7.20 (H-2‴). Characteristic resonances of a methyl group at δ_H 1.12 (d, *J* = 6.4 Hz, CH_3) and of anomeric hydrogen at δ_H 5.23 (d, *J* = 1.2 Hz, H-1″) suggested the presence of a rhamnose moiety; a second doublet corresponding to anomeric hydrogen of a glucose moiety was observed at δ_H 4.39 (d, *J* = 7.6 Hz, H-1′). A *trans*-coupled olefinic pair of doublets were observed at δ_H 6.49 and 7.67 (d, *J* = 16.0 Hz), which together with the aromatic hydrogen atom resonances indicated the presence of an isoferuloyl moiety. An AA′BB′ pattern of an ethylene group was observed at δ_H 2.83 (2H, t, *J* = 6.8 Hz), 3.75 (1H, m), and 4.07 (1H, m), corresponding to a glycosidically bound phenethyl unit (Figure 1) [36]. In addition, two methoxy proton signals at δ_H 3.81 (3H, s) and 3.89 (3H, s) were also detected in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum of compound **3** contained 31 carbon signals. The signals comprised methoxy

groups, sugar moieties, aromatic carbons, oxygen-bearing carbons and carbonyl functionality (Figure 1). The ^{1}H-NMR spectrum of compound **3** was similar to that of acteoside [37]; however, the hydroxyl groups at C-4 and C-4‴ of acteoside were replaced by two methoxy groups of **3**. Based on the above analysis, the structure of compound **3** was elucidated as 3-hydroxy-4-methoxyphenethyl-*O*-α-L-rhamnopyranosyl-(1″→ 3′)-4′-*O*-isoferuloyl-*β*-D-glucopyranoside, named martinoside [38]. This is the first isolation of martinoside from *S. indica*. Martinoside exhibits anticancer [39, 40] and cytotoxic activities [41].

4. Conclusions

The methanol extract from the whole plant of *S. indica* was partitioned into hexane, ethyl acetate, butanol-soluble fractions, and a water layer. Three compounds, naringenin (**1**), arctiin (**2**), and martinoside (**3**) were isolated from the ethyl acetate fraction. Their chemical structures were determined by the interpretation of NMR spectral data and comparison with published data. Arctiin (**2**) and martinoside (**3**) were isolated from *S. indica* for the first time.

Declaration of Competing Interest

The authors declare no competing interests.

Author contributions

NVH, TNTV designed and planned the experiments. NTN, DTBH implemented the experiments. NTN, DCT investigated the data and wrote the manuscript. All the authors agreed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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