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PHENOLIC GLYCOSIDE CONSTITUENTS FROM THE RHIZOMES OF *ATRACTYLODES MACROCEPHALA* KOIDZ

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Summary

Phenolic Glycoside Constituents from the Rhizomes of *Atractylodes macrocephala* Koidz

Four compounds were isolated from *Atractylodes macrocephala* rhizomes as syringin (**1**), syringaresinol-4-*O*-*β*-D-glucoside (**2**), *ent*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-*β*-D-glucopyranoside (**3**), *syn*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-*β*-D-glucopyranoside (**4**). Their structures were elucidated by ESI-MS, NMR spectroscopic evidence and in comparison with published data. Compounds **2**, **3**, and **4** have been isolated from this plant for the first time.

Keywords: *Atractylodes macrocephala*; Asteraceae; *Syringin, Syringaresinol-4-O-β-D-glucoside, Picraquassioside C.*

1. Introduction

Atractylodes macrocephala rhizomes is one of the most highly used medicinal plants in East Asia and it has been used treatment diarrhea, peptic ulcer disease [1]. Up to now, more than 200 secondary compounds have been isolated from the plant [2]. A lot of research indicated that *A. macrocephala* rhizomes had various bioactivities, including antibacterial, anti-inflammatory, anti-tumor, anti-cancer, immunomodulatory, and other activities.

Previous studies were also demonstrated that sesquiterpenes, polyacetylenes together with their glycosides were the main chemical components and were responsible for creating the biological activities of this plant [1],[2],[3],[4],[5],[6],[7]. In this study, we found three lignan glycosides and one phenylpropanoid glycoside from *A. macrocephala* rhizomes.

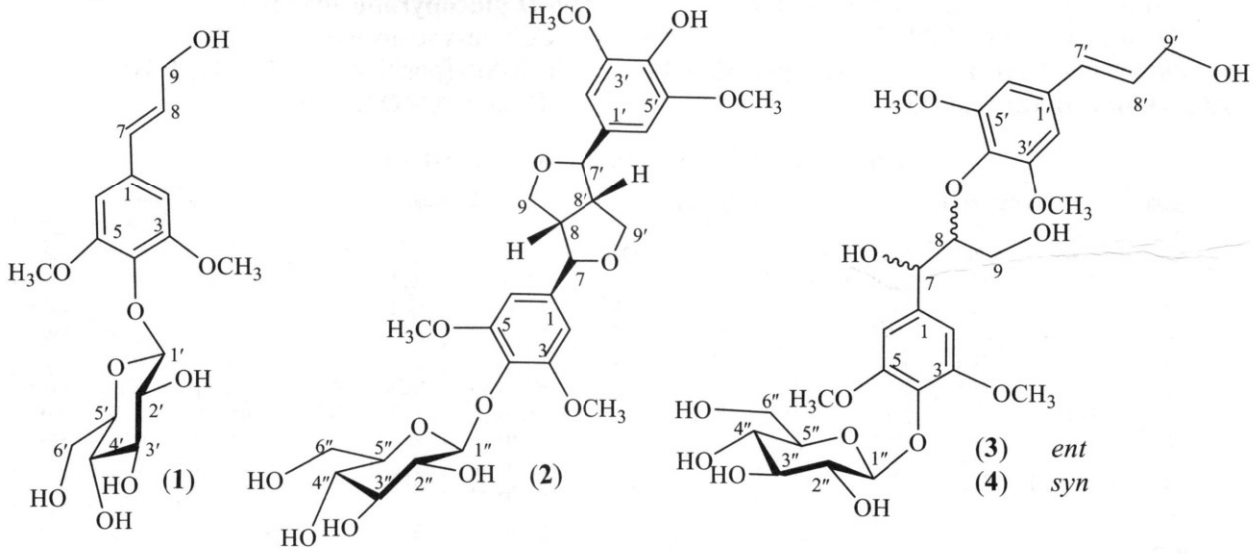

Fig. 1. Structure of compounds **1-4**

2. Experimental

2.1. General procedures

ESI-MS: Agilent LC-MSD-Trap SL. ^{1}H-NMR (500 MHZ) and ^{13}C-NMR (125 MHZ) spectral data were measured on a Bruker Avance 500 Ultrashield NMR Spectrometer at 25°C. Chemical shifts were reported as δ values with reference to TMS as the internal standard for ^{1}H (δ = 0 ppm). TLC: *Silica gel* 60 F_{254} (0.25mm, Merck); reversed phase $RP18F_{254S}$ (0.25mm, Merck). CC: *Silica gel* 60 (230-400 mesh, Merck) for the first column, *silica gel* 60, 40-63 μm (Merck) for the following columns. Optical rotations were recorded in a JASCO P-2000 polarimeter.

2.2. Plant materials

The *Atractylodes macrocephala* Koidz rhizomes were collected in May. 2021 in

Quan Ba district - Ha Giang province and identified by Dr. Nguyen The Cuong, Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology. This plant was grown in Quan Ba district - Ha Giang province. The voucher specimens (code: Ha Giang 06) were deposited at the Agro-Pharmaceutical Department, Center for Research and Technology Transfer, Vietnam Academy of Science and Technology.

2.3. Extraction and isolation

The powder of *A. macrocephala* Koidz rhizomes (2.5 kg) were extracted with methanol at room temperature (3 times, each overnight). After concentrating under reduced pressure to give 200.1 gram crude extract was suspended in 1.000 mL and then sequentially partitioned with dichloromethane. The organic solvent was evaporated in *vacuum* to afford CH_2Cl_2 (45.02 g). Water layer was loaded on the diaion column with a solvent system as MeOH:H_2O (0:100 to 100:0, v:v) to yield 3 fractions as AMW1, AMW2 and AMW3. Fraction AMW3 was separated on a *silica gel* column, eluting with a gradient of CH_2Cl_2:MeOH (100:1 to 0:100, v:v) to give 2 fractions as AMWB1.10 and AMWB1.11. Fraction AMWB1.11 was separated on a *silica gel* column, eluting with solvent systems CH_2Cl_2:MeOH:H_2O (10:1:0.01, v:v:v) to afford 3 fractions as AMWB2.4, AMWB2.7, AMWB2.9. Fraction AMWB2.4 was subjected to *silica gel* column chromatography with a mobile phase as CH_2Cl_2:CH_3COCH_3 (1:1, v:v) to give a fraction AMWB 3.4. Fraction AMWB3.4 was separated on a sephadex LH20 column solvent system as CH_3OH:H_2O (1:2, v:v) to a obtain **2** (9.7 mg). Fraction AMWB2.7 was further purified on an RP-18 column using the solvent system CH_3COCH_3:H_2O (1:6, v:v) to yield **3** (9.3 mg) and **1** (4.2 mg). Fraction AMWB2.9 was separated on an RP-18 column with a mobile phase as CH_3COCH_3:H_2O (1:6, v:v) to afford **4** (8.0 mg).

Syringin (1)

Colorless semisolid

Melting point: 191-192°C

$[\alpha]_D$ = - 18.0° (H_2O)

ESI-MS (positive): *m/z* 373.4 $[M+H]^+$

^{1}H- and ^{13}C-NMR: Table 1

Syringaresinol-4-*O*-*β*-D-glucopyranoside (2)
Amorphous powder
Melting point: 170 - 173°C
$[\alpha]^{20}_D$ = –21.5 (c 0.20, MeOH)
ESI-MS (positive): *m/z* 581.1 $[M+H]^+$
^{1}H- and ^{13}C-NMR: Table 1

***ent*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-*β*-D-glucopyran*oside* (3)**
Colorless semisolid
ESI-MS (positive): *m/z* 599.6 $[M+H]^+$
^{1}H- and ^{13}C-NMR: Table 1

***syn*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-*β*-D-glucopyranoside (4)**
Colorless semisolid
ESI-MS (positive): *m/z* 599.4 $[M+H]^+$
^{1}H- and ^{13}C-NMR: Table 1.

Table 1. ^{1}H and ^{13}C-NMR data of compounds **1-4** in CD_3OD

Position	Compound 1			Compound 2			Compound 3			Compound 4		
	δ_H	δ_C	δ_C*	δ_H	δ_C	δ_C**	δ_H	δ_C	δ_C***	δ_H	δ_C	δ_C****
1	-	135.9	136.3	-	139.5	139.6	-	139.3	139.2	-	139.5	139.7
2	6.77 (1H, s)	105.5	105.9	6.74 (1H, s)	104.9	104.9	6.82 (1H, s)	105.8	105.7	6.77 (2H, s)	105.7	106.0
3	-	154.4	154.7	-	154.4	154.5	-	153.8	153.7	-	153.8	153.4
4	-	135.3	135.7	-	135.6	135.7	-	135.5	135.4	-	135.6	135.2
5	-	154.4	154.7	-	154.4	154.5	-	153.8	153.7	-	153.8	153.4
6	6.77 (1H, s)	105.5	105.9	6.74 (2H, s)	104.9	104.9	6.82 (1H, s)	105.8	105.7	6.77 (2H, s)	105.7	106.0
7	6.58 (1H, t)	131.3	131.7	4.79 (1H, d)	87.2	87.2	5.03 (1H, d)	74.0	74.0	4.95 (1H, d)	74.0	73.6
8	6.35 (1H, dt)	130.0	130.5	3.16 (2H, m)	55.7	55.7	4.25 (1H, m)	88.0	87.9	4.30 (1H, dd)	87.0	87.6
9	4.24 (2H, dd)	63.6	64.0	4.30 (1H, m) 3.94 (1H, dd)	72.9	72.9	3.85 (1H, m) 3.49 (1H, m)	61.9	61.9	3.95 (1H, m) 3.62 (1H, m)	61.6	61.2
3-OCH_3	3.88 (3H, s)	57.0	57.4	3.87 (3H, s)	57.1	56.8	3.86 (3H, s)	57.0	56.9	3.83 (3H, s)	57.0	**56.5**
5-OCH_3	3.88 (3H, s)	57.0	57.4	3.87 (6H, s)	57.1	56.8	3.86 (6H, s)	57.0	56.9	3.83 (3H, s)	57.0	**56.5**
1'				-	133.0	133.1	-	134.8	134.7	-	134.7	133.8
2'				6.67 (1H, s)	104.6	104.5	6.73 (1H, s)	104.8	104.7	6.75 (1H, s)	104.9	104.4
3'				-	149.3	149.5	-	154.2	154.2	-	154.5	153.9
4'				-	136.3	136.3	-	136.9	136.8	-	136.4	136.2
5'				-	149.3	149.5	-	154.2	154.2	-	154.5	153.9
6'				6.67 (2H, s)	104.6	104.5	6.73 (1H, s, H-6')	104.8	104.7	6.75 (1H, s)	104.9	104.4
7'				4.74 (1H, d)	87.6	87.6	6.57 (1H, brd)	131.3	131.2	6.55 (1H, brd)	131.3	131.2
8'				3.16 (1H, m)	55.5	55.5	6.35 (1H, dt)	130.0	129.9	6.35 (1H, dt)	129.9	129.3
9'				4.30 (1H, m) 3.94 (2H, dd)	72.9	72.9	4.25 (2H, m)	63.5	63.5	4.25 (2H, t)	63.5	**62.7**
3'-OCH_3				3.86 (3H, s)	56.9	57.0	3.87 (3H, s)	56.6	56.6	3.86 (3H, s)	56.7	**56.2**
5'-OCH_3				3.86 (3H, s)	56.9	57.0	3.87 (3H, s)	56.6	56.6	3.86 (3H, s)	56.7	**56.2**
Glc-1"	4.89 (1H, d)	105.4	105.8	4.88 (1H, d)	105.4	105.4	4.80 (1H, d)	105.7	105.6	4.80 (1H, overlap)	105.6	105.3
2"	3.50 (1H, m)	75.7	76.0	3.50 (1H, m)	75.7	75.7	3.49 (1H, m)	75.7	75.7	3.50 (1H, m)	75.7	76.1
3"	3.44 (1H, m)	77.8	78.1	3.44 (1H, m)	77.8	77.8	3.42 (1H, m)	77.8	78.1	3.44 (1H, m)	77.8	78.4
4"	3.41 (1H, m)	71.3	71.6	3.42 (1H, m)	71.3	71.3	3.44 (1H, m)	71.4	71.3	3.43 (1H, m)	71.4	71.6
5"	3.22 (1H, m)	78.4	78.6	3.22 (1H, m)	78.3	78.4	3.23 (1H, m)	78.4	78.3	3.22 (1H, m)	78.4	78.6
6"	3.81 (1H, dd) 3.69 (1H, dd)	62.6	63.0	3.80 (1H, dd) 3.69 (1H, dd)	62.6	62.6	3.79 (1H, m) 3.69 (1H, dd)	62.6	62.5	3.87 (1H, m) 3.70 (1H, m)	62.6	62.6

*δ_C of syringin (125 MHz, CD_3OD) [8], **δ_C of Syringaresinol-4-*O*-*β*-D-glucopyranoside (125 MHz, CD_3OD) [10], ***δ_C of Picraquassioside C (150 MHz, CD_3OD) [12], ****δ_C of Picraquassioside C (150 MHz, C_5D_5N) [13].

3. Results and discussion

Compound **1** was obtained as a colorless semisolid from the water layer. The molecule formula was determined to be $C_{17}H_{24}O_9$ based on the molecular ion positive peak ESI-MS at *m/z* 373.4 $[M+H]^+$. The ^{1}H-NMR spectrum showed characteristic signals of two *trans*-olefinic protons at δ_H 6.58 (1H, t, J = 15.5 Hz, H-7) and 6.35 (1H, dt, J = 15.5, 6.0 Hz, H-8) and two aromatic protons at δ_H 6.77 (2H, s, H-2, H-6). The signals of two methoxy groups at δ_H 3.88 (6H, s, 3-OCH_3, 5-OCH_3), and a down-field shifted methylene at δ_H 4.24 (2H, dd, J = 6.0, 1.5 Hz, H-9) were recognized. Additionally, an *anomeric*-proton signal was observed at δ_H 4.89 (1H, d, J = 7.5 Hz, H-1′) and ^{13}C-NMR were confirmed the presence of a *β*-glucopyranosyl moiety. Analysis of the ^{13}C NMR spectrum of **1** revealed the presence of an aromatic ring at δ_C 154.4 (C-3), 154.4 (C-5),135.9 (C-1), 135.3 (C-4), 105.5 (C-2), 105.5 (C-6), an allyl at δ_C 131.3 (C-7), 130.0 (C-8), 63.6 (C-9), a glucopyranosyl moiety at δ_C 105.4 (C-1′), 78.4 (C-5′), 77.8 (C-3′), 75.7 (C-2′), 71.3 (C-4′), 62.6 (C-6′) and two methoxyl groups at δ_C 57.0 (C-3/C-5,

OCH_3). Analyzing the NMR spectra of **1** combined with knowledge of its chemotaxonomy and comparison with the literature [8], **1** was suggested as syringin. This compound was isolated from this plant [9].

Compound **2** was obtained as an amorphous powder from the water layer. The ESI-MS of **2** showed a molecular ion at *m/z* 581.1 $[M+H]^+$ and 1D, 2D-NMR spectra, consistent with the formula of $C_{28}H_{36}O_{13}$. Its ^{1}H-NMR spectrum appeared signals of four aromatic protons at δ_H 6.74 (2H, s, H-2/H-6), 6.67 (2H, s, H-2′/H-6′) and characteristic signals of two tetrahydrofuran rings at δ_H 4.79 (1H, d, J = 4.5 Hz, H-7), 4.74 (1H, J = 4.5 Hz, H-7′), 4.30 (2H, m, H-9b, H-9′b), 3.94 (2H, dd, J = 9.0, 3.0 Hz, H-9a, H-9′a), 3.16 (2H, H-8, H-8′) together with signals for four methoxy groups at δ_H 3.87 (6H, s, 3-OCH_3, 5-OCH_3), 3.86 (6H, s, 3′-OCH_3, 5′-OCH_3). In addition, an *anomeric*-proton signal was recognized at δ_H 4.88 (1H, d, J = 7.5 Hz, H-1″). Analysis combined ^{13}C-NMR and HSQC spectra displayed the signals of twenty-eight carbon including two benzene rings at δ_C 154.4 (C-3), 154.4 (C-5), 149.3 (C-5′), 149.3 (C-3′), 139.5 (C-1), 136.3 (C-4′), 135.6 (C-4), 133.0 (C-1′), 104.9 (C-2), 104.9 (C-6), 104.6 (C-2′), 104.6 (C-6′), two tetrahydrofuran rings at δ_C 87.6 (C-7′), 87.2 (C-7), 72.9 (C-9), 72.9 (C-9′), 55.7 (C-8), 55.5 (C-8′), four methoxys at δ_C 57.1 (3-OCH_3), 57.1 (5-OCH_3), 56.9 (3′-OCH_3), 56.9 (5′-OCH_3) and carbon signals for a β-glycopyranosyl moiety at δ_C 105.4 (C-1″), 78.3 (C-5″), 77.8 (C-3″), 75.7 (C-2″),71.3 (C-4″), 62.6 (C-6″). The HMBC correlations from H-1″ δ_H 4.88 (1H, d, J = 7.5 Hz, H-1″) to C-4 δ_C 135.6 (C-4) and proton of methoxy groups [δ_H 3.87 (6H, s, 3-OCH_3, 5-OCH_3)] to C-3, C-5 [δ_C 154.4 (C-3), 154.4 (C-5)] were observed. These data contributed to the determination of the positions of four methoxy groups attached to C-3, C-5, C-3′ C-5′ and a β-glycopyranosyl moiety located at C-4. Therefore, the structure of **2** was elucidated as syringaresinol-4-*O*-β-D-glucoside when compared with the spectral data in the literature [10]. This compound was reported from this plant for the first time.

Compound **3** was obtained as a colorless semisolid from the water layer. The molecular formula of **3** was deduced as $C_{28}H_{38}O_{14}$ by the ESI-MS ion peak at *m/z* 599.6 $[M+H]^+$ and ^{13}C-NMR. The ^{1}H-NMR spectrum showed that two signals of the benzene ring at δ_H 6.82 (2H, s, H-2, H-6), 6.73 (2H, s, H-2′, H-6′) together with two signals of *trans*-olefinic protons at δ_H 6.57 (1H, br d, J = 16.0 Hz, H-7′), 6.35 (1H, dt, J = 16.0, 5.5 Hz, H-8′). The characteristic signal of an *anomeric*-proton at δ_H 4.80 (1H, d, J = 7.5 Hz, H-1″) was demonstrated the presence of a β-glycopyranosyl moiety. Besides, four signals of methoxy groups were recognized at δ_H 3.87 (6H, s, 3′, 5′- OCH_3), 3.86 (6H, s, 3, 5- OCH_3). The ^{13}C-NMR and HSQC spectra were observed the presence of twenty-eight carbon signals including eight quaternary carbons, thirteen methines, three methylenes and four methoxys. The HMBC correlations observed between H-1″ [δ_H 4.80 (1H, d, J = 7.5 Hz, H-1″)], H-2, H-6 [δ_H 6.82 (2H, s, H-2, H-6)] and C-4 (δ_C 135.5) indicated that the linkage position of β-D-glycopyranosyl located at C-4. In addition, the correlations from H-7′, H-8′ [δ_H 6,57 (1H, br d, J = 16.0 Hz, H-7′), 6.35 (1H, dt, J = 16.0, 5.5 Hz, H-8′)] to C-1′ (δ_C 134.8), from H-2′, H6′ [δ_H 6.73 (2H, s, H-2′, H-6′)] to C-4′ (δ_C 136.9) were confirmed allyl alcohol moiety at C-1′. The *ent*- configuration of **3** at C-7 and C-8 was determined by the coupling constant $J_{7,8}$-value (5.0 Hz) in the ^{1}H-NMR spectrum [11] Comparison of their NMR data with those reported [12] in the literatures **3** was identified *ent*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-β-D-glucopyran*oside*. This is the first time this compound has been isolated from *Atractylodes macrocephala* rhizomes. It *belongs to the class* of organic as phenolic glycosides.

Compound **4** was isolated as a colorless semisolid from the water layer of *A. macrocephala* rhizomes. The ^{1}H and ^{13}C-NMR spectra of compound **4** were similar to those of **3** with some differences being that the chemical shift of H-7 and C-8 in **3** changed from downfield at δ_H 5.03 (1H, d, J = 5.0 Hz, H-7), δ_C 88.0 (C-8) to upfield in **4** at δ_H 4.95 (1H, d, J = 5.5 Hz, H-7); δ_C 87.0 (C-8). Contrarily, H-8 in **3** changed from upfield at δ_H 4.25 (1H, m, H-8) to downfield in **4** at δ_H 4.30 (1H, dd, J = 9.0, 5.0 Hz H-8). The *syn*-configuration of **4** at C-7 and C-8 was identified by the coupling constant $J_{7,8}$-value (5.5 Hz) in the ^{1}H-NMR spectrum [13]. Further analyses NMR data of **4** and comparison with literature [13] suggested that compound **4** was *syn*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-β-D-glucopyranoside.

4. Conclusion

From water extraction of *Atractylodes macrocephala* Koid rhizomes was isolated some glycosides compound by column chromatography methods. Their structures were identified as syringin (**1**), syringaresinol-4-*O*-β-D-glucoside (**2**), *ent*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-β-D-glucopyranoside (**3**), *syn*-syringylglycerol-8-*O*-4′-sinapyl ether 4-*O*-β-D-glucopyranoside (**4**).

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PHENOLICS AND ALKALOIDS FROM THE FRUITS OF *PIPER LONGUM* L.

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Summary

Phenolics and Alkaloids from the Fruits of *Piper longum* L.

Seven compounds, including avenalumic acid methyl ester (**1**), methyl piperate (**2**), piperine (**3**), pipernonaline (**4**), (2*E*,4*Z*,8*E*)-*N*-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl] piperidine (**5**), pipercide (**6**), and guineensine (**7**) were isolated from the ethyl acetate extract of *Piper longum* L. fruits. The structures of these compounds were identified by using extensive nuclear magnetic resonance spectroscopy (NMR) data, mass spectrometry (MS), and comparing with published literature. Compounds **1** and **6** were the first report from this species.

Keywords: *Piper longum, Fruit, Phenolics, Alkaloids, Piperine.*

1. Introduction

Piper longum L., a species of Piperaceae [1], distributes mainly in India, South China, Laos, Vietnam, and some other countries in Southeast Asia. In Vietnam, *P. longum* grows in mountainous and midland provinces, especially those with limestone mountains [2]. According to traditional medicine, *P. longum* is hot, pungent, and is often used to treat respiratory diseases such as sinusitis, pain in the nostrils, and nasal cavity… and digestive diseases such as abdominal pain, cold stomach causing vomiting, diarrhea, indigestion... [1],[2]. Studies on chemical composition in the *P. longum* fruits showed a large number of alkaloids and related compounds [3],[4]. In addition, *P. longum* contains lignans, essential oils, and organic acids [3],[4]. Biological investigation of extracts and compounds from *P. longum* fruits showed anti-cancer [5],[6], immunomodulation [7], antioxidant [8], hepatoprotection [8],[9], anti-inflammation [10],[11], and antibacterial effects [12]. Piperine, an alkaloid found in plants such as *P. nigrum* and *P. longum*, shows anti-lung cancer and metastatic activity. Piperlonguminin inhibits α-MSH-induced tyrosinase synthesis [5],[6]. Besides, *P. longum* extracts and piperinic acid decreased dose-dependently lympho cell ($CD4^+$ and $CD8^+$ cells) and cytokine levels in Balb/C mice [7]. To our knowledge, until now no report about the chemical composition of this species collected in Vietnam has been published. In this paper, we report the isolation and structural elucidation of phenolics and alkaloids compounds from the fruits of *P. longum*.

2. Materials and methods

2.1. Plant material

Samples of *Piper longum* L., Piperaceae were collected in Dak Song, Dak Nong, Vietnam in September 2020. The plant was identified by Assoc. Prof. Pham Thanh Huyen and MSc. Nguyen Van Hieu (National Institute of Medicinal Materials,