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Extraction Of Phenolic Constituents From *Perilla frutescens* And Their Xanthine Oxidase Inhibitory Activity

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***Abstract*—Six phenolic compounds including rosmarinic acid, luteolin 4′-*O*-*β*-glucopyranoside, apigenin, apigenin 7-*O*-*β*-rutinoside, myricetin 3-*O*-*α*-arabinopyranoside, and myricetin 3-*O*-*β*-galactopyranoside were isolated from the leaves and twigs of *P. frutescens* by chromatographic techniques. Their chemical structures were determined by extensive analysis of NMR spectral data as well as comparison with those in the literature. These compounds exhibited xanthine oxidase inhibitory activity with IC_{50} values ranging of 8.3 – 47.0 µM. The results indicated that phenolic components from *P. frutescens* could be active ingredients for the treatment of hyperuricemia.**

Keywords — Perilla frutescens; phenolic composition; isolation; xanthine oxidase inhibitory activity; hyperuricemia.

I. INTRODUCTION

Perilla frutescens (L.) Britton (Lamiaceae family) is an annual herbaceous plant, widely cultivated in European and Asian countries. It is an edible and medicinal plant which used for treatment of cold and asthma, lowering blood lipid levels, and anti-inflamation [1]. Its seed is an important source for production of perilla oil and the fresh leaf is popular flavor vegetable in East Asia [2]. Phytochemical studies of *P. frutescens* identified several types of compounds including alkaloids, phenolic acids, flavonoids, and terpenoids [1-3]. Recent pharmacological studies indicates that phytocomponents from *P. frutescens* potentially showed anti-hyperuricemia activity [4-6]. In contribution to clarify active ingredients, this paper describes the extraction and identification of several chemical components from the leaves and twigs of *P. frutescens*. Their anti-hyperuricemia property are evaluated by inhibition of xanthine oxidase activity.

II. MATERIALS AND METHODS

A. General experiment procedures

The NMR spectra were measured on a Bruker AvanceNEO 600 MHz or a Bruker AvanceIII 500 MHz. Thin layer chromatography was carried out using precoated plates (Silica gel 60 F_{254} and/or Silica gel 60 RP18 F_{254S}). Open column chromatography was performed using silica gel (particle size 40–63 µm), ODS reversed phase resin (particle size 150 µm), diaion HP-20 resin, and sephadex LH-20 gel. Semi-preparative HPLC was acquired on an Agilent 1100 system including autosampler, quaternary pump, DAD detector, and equipped with YMC J′sphere ODS-H80 HPLC column (20×250 mm, particle size 4µm). Isocratic solvent system was used at a flow rate of 3 mL/min and detector acquisition was set at 210 and 254 nm. Organic solvents were used at technical grade, except HPLC grade solvents using for semi-preparative HPLC.

B. Plant materials

The leaves and twigs of *Perilla frutescens* (L.) Britton were collected at Hanoi, Vietnam in February 2025. The fresh samples were air dried and pulverized into fine powder.

C. Extraction and isolation

The dried and powdered leaves and twigs of *P. frutescens* (5.0 kg) were extracted with methanol for three times (each time using 10 L methanol, extraction in 1 hour in an ultrasonic bath at room temperature). The methanol solutions were filtered and the solvent were evaporated in vacuum to give methanol extract (160 g). This crude extract was then suspended with distilled water (2.0 L) and then successively separated with dichloromethane and ethyl acetate to give corresponding solvent soluble fractions and water layer. The water layer was loaded on a diaion HP20 column, washed with water (1.5 L), and then eluted with methanol/water (stepwise 1/3, 1/1, 3/1, and 1/0, v/v) to give four fractions, PFW1–PFW4. Fraction PFW2 (25 g) was subjected on a silica gel column chromatography and then eluted with gradient solvent system of dichloromethane/methanol (0-100% volume of methanol) to give four fractions, PFW2A– PFW2D. Fraction PFW2A was firstly chromatographed on a reversed phase C18 (RP18) column, eluting with methanol/water (2/3, v/v) and then purified by semi preperative HPLC using acetonitrile/water (40% acetonitrile) to give compound **4** (15 mg). Fraction PFW2C was also chromatographed on a reversed phase C18 (RP18) column, eluting with methanol/water (1/2, v/v) to give three subfractions, PFW2C1– PFW2C3. Subfraction PFW2C1 was purified by semi preperative HPLC using acetonitrile/water (34% acetonitrile) to give compound **1** (21 mg). Fraction PFW4 (11 g) was loaded on a

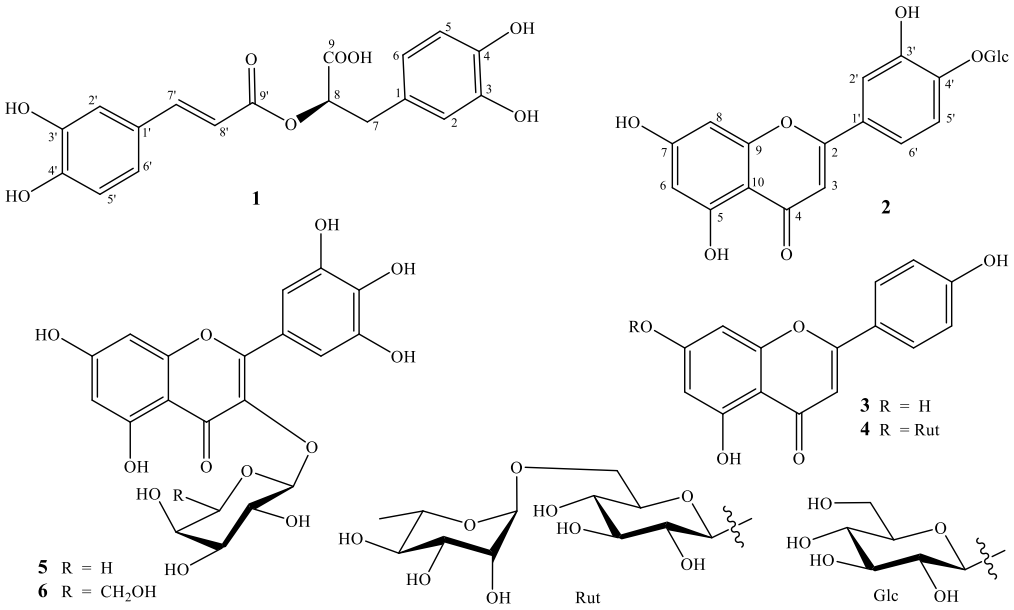

Fig. 1. *Several phenolic constituents isolated from the leaves and twigs of Perilla frutescens*

silica gel column and eluted with dichloromethane/methanol/water (5/1/0.1, v/v/v) to give five fractions, PFW4A–PFW4E. Fraction PFW4A was further fractionated on an RP18 column chromatography, eluting with methanol/water (2/1, v/v) to give two fractions, PFW4A1 and PFW4A2. Fraction PFW4A2 was purified by semi-preparative HPLC using acetonitrile/water (56% acetonitrile) to give compound **3** (7 mg). Fraction PFW4C was subjected on an RP18 column chromatography, eluting with acetone/water (2/5, v/v) to give three fractions, PFW4C1–PFW4C3. Fraction PFW4C2 was purified by semi-preparative HPLC using acetonitrile/water (38% acetonitrile) to give compound **2** (14 mg). Fraction PFW4C3 was purified by semi-preparative HPLC using acetonitrile/water (35% acetonitrile) to give compound **5** (18 mg). Fraction PFW4D was loaded on an RP18 column chromatography, eluting with methanol/water (1/2, v/v) to give two fractions, PFW4D1 and PFW4D2. Fraction PFW4D1 was firstly chromatographed on a sephadex LH-20 column, eluting with methanol/water (1/1, v/v) and then purified by semi-preparative HPLC using acetonitrile/water (30% acetonitrile) to give compound **6** (10 mg).

- (*R*)-Rosmarinic acid (**1**): Molecular formula: $C_{18}H_{16}O_8$; Pale yellow amorphous powder; $[\alpha]_D^{28}$: +32 (*c* = 0.1, MeOH); ^{1}H-NMR and ^{13}C-NMR data are given in Table I.

- Luteolin 4′-*O*-*β*-glucopyranoside (**2**): Molecular formula: $C_{21}H_{20}O_{11}$; Pale yellow amorphous powder; ^{1}H-NMR and ^{13}C-NMR data are given in Table I.

- Apigenin (**3**): Molecular formula: $C_{15}H_{10}O_5$; Pale yellow amorphous powder; ^{1}H-NMR and ^{13}C-NMR data are given in Table I.

- Apigenin 7-*O*-*β*-rutinoside (**4**): Molecular formula: $C_{27}H_{30}O_{14}$; White amorphous powder; ^{1}H-NMR and ^{13}C-NMR data are given in Table II.

- Myricetin 3-*O*-*α*-arabinopyranoside (**5**): Molecular formula: $C_{20}H_{18}O_{12}$; Pale yellow amorphous powder; ^{1}H-NMR and ^{13}C-NMR data are given in Table II.

- Myricetin 3-*O*-*β*-galactopyranoside (**6**): Molecular formula: $C_{21}H_{20}O_{13}$; Pale yellow amorphous powder; ^{1}H-NMR and ^{13}C-NMR data are given in Table II.

D. Xanthine oxidase inhibitory activity assay

Xanthine oxidase activity assay was performed using xanthine as the substrate, as previously described [7]. The samples were dissolved in dimethyl sulfoxide at a concentration of 10 mM and diluted with buffer to the required concentrations. A solution of xanthine oxidase (100 µL, 0.03 U/mL) in phosphate buffer (50 mM, pH 7.5) was mixed with a 50 µL solution of samples in 96-well plates. The plate was incubated for 5 minutes at 37°C, and then the reaction was initiated by adding 50 µL of a solution of xanthine (0.60 mM) to each well. The absorbance of the reaction mixture at 295 nm was recorded every minute for 10 consecutive minutes by microplate reader (Infinite 200Pro, Tecan Group Ltd.). Buffer and allopurinol were used as a vehicle and positive control, respectively. The xanthine oxidase inhibitory activity was calculated by the difference in absorbance between samples and control wells. The IC_{50} (half maximum inhibitory concentration) value was generated by GraphPad Prism 8.0 software

III. Results and Discussion

The powdered leaves and twigs of *P. frutescens* was extracted with methanol and then separated with dichloromethane, ethyl acetate to give solvent solube fractions and water. The water layer was then fractionated by flash column chromatography and finally purified by semi-preparative HPLC to give six compounds **1**–**6** (Fig. 1).

Compound **1** was isolated as a pale yellow amorphous powder. The ^{1}H-NMR spectrum of **1** contained signals corresponding for six protons of two sets of ABX aromatic proton coupled systems [δ_H 6.77 (1H, br s), 6.64 (1H, d, *J* = 8.0 Hz), 6.71 (1H, br d, *J* = 8.0 Hz), 7.06 (1H, br s), 6.80 (1H, d, *J* = 8.0 Hz), 6.97 (1H, br d, *J* = 8.0 Hz)], two *trans*-coupled olefinic protons [δ_H 7.57 (1H, d, *J* = 16.0 Hz) and 6.29 (1H, d, *J* = 16.0 Hz)], a methylene group [δ_H 3.12 (1H, dd, *J* = 4.0 and 14.5 Hz) and 3.02 (1H, dd, *J* = 8.5 and 14.5 Hz)] coupled with an oxygenated methine [δ_H 5.21 (1H, dd, *J* = 4.0 and 8.5 Hz)]. The ^{13}C-NMR spectrum of **1** revealed signals of 18 carbons including two carbonyl carbons (δ_C 173.7 and 168.5), 14 sp^2 hybridized carbons (δ_C 115.2 to 149.6), an oxygenated carbon (δ_C 74.7) and a saturated methylene carbon (δ_C 37.9). Of these, a carbonyl carbon, two *trans*-coupled olefinic protons, and an ABX coupled proton system suggested the presence of *trans*-caffeoyl moiety. The remaining proton and carbon signal including another ABX coupled proton system, a carbonyl carbon, and an oxygenated methine group in coupling with a methylene group indicated for the structural fragment of 8-hydroxydihydrocaffeoyl moiety. Moreover, the desheilded signal of H-8 (δ_H 5.21) and C-8 (δ_C 74.7) suggested for the esterification at C-8. These NMR evidence and the its positive optical rotation value indicated compound **1** to be (*R*)-rosmarinic acid [8]. This compound has been previouly isolated from this plant, showing various biological activity such as antioxidant, anti-inflammation, anti-obesity, anti-hyperglycemia, and xanthine oxidase inhibitory activity [9-14].

TABLE I. ^{1}H- AND ^{13}C-NMR SPECTROSCOPIC DATA OF COMPOUNDS **1** – **3**

No.	[g] **1**		No.	[g] **2**		[h] **3**	
	[a] δ_C	[b] δ_H (mult., *J* in Hz)		[c] δ_C	[d] δ_H (mult., *J* in Hz)	[e] δ_C	[f] δ_H (mult., *J* in Hz)
1	129.3	-	2	165.5	-	163.0	-
2	117.5	6.77 (br s)	3	105.1	6.62 (s)	100.2	6.78 (s)
3	145.2	-	4	183.8	-	181.8	-
4	146.1	-	5	163.0	-	161.2	-
5	121.8	6.64 (d, 8.0)	6	100.3	6.23 (d, 1.8)	99.7	6.19 (d, 2.0)
6	116.5	6.71 (br d, 8.0)	7	166.3	-	164.5	-
7	37.9	3.02 (dd, 8.5, 14.5) 3.12 (dd, 4.0, 14.5)	8	95.1	6.46 (d, 1.8)	94.8	6.48 (d, 2.0)
8	74.7	5.21 (dd, 4.0, 8.5)	9	159.9	-	157.0	-
9	173.7	-	10	105.4	-	103.2	-
1′	127.6	-	1′	127.2	-	119.1	-
2′	114.4	7.06 (br s)	2′	114.9	7.45 (d, 1.8)	121.5	7.92 (d, 8.0)
3′	149.6	-	3′	148.7	-	116.0	6.90 (d, 8.0)
4′	146.7	-	4′	150.0	-	161.1	-
5′	116.3	6.80 (d, 8.0)	5′	118.0	7.34 (d, 7.8)	116.0	6.90 (d, 8.0)
6′	123.1	6.97 (br d, 8.0)	6′	119.8	7.17 (dd, 1.8, 7.8)	121.5	7.92 (d, 8.0)
7′	147.6	7.57 (d, 16.0)	1″	103.2	4.96 (d, 7.8)		12.90 (s, 5-OH)
8′	115.2	6.29 (d, 16.0)	2″	74.8	3.58 (dd, 7.8, 9.0)		
9′	168.5	-	3″	77.6	3.53 (t, 9.0)		
			4″	71.3	3.45 (t, 9.0)		
			5″	78.5	3.51 (m)		
			6″	62.4	3.95 (dd, 2.4, 12.0) 3.76 (dd, 5.4, 12.0)		

Measured at [a]125 MHz, [b]500 MHz, [c]150 MHz, [d]600 MHz, [e]100 MHz, [f]400 MHz, [g]CD_3OD, [h]DMSO-d_6

Compound **2** was isolated as a pale yellow amorphous powder. The ^{1}H-NMR spectrum of **2** showed signals including an ABX aromatic coupled protons [δ_H 7.45 (1H, d, *J* = 1.8 Hz), 7.34 (1H, d, *J* = 7.8 Hz), 7.17 (1H, dd, *J* = 1.8 and 7.8 Hz)], an AX aromatic coupled protons [δ_H 6.23 (1H, d, *J* = 1.8 Hz) and 6.46 (1H, d, *J* = 1.8 Hz)], a olefinic proton [δ_H 6.62 (1H, s)], an anomeric proton [δ_H 4.96 (1H, d, *J* = 7.8 Hz)], and carbinol protons (δ_H 3.45 – 3.95). The ^{13}C-NMR spectrum of **2** observed signals of 21 carbons. Of these, Fitteen sp^2 hybridized carbons (δ_C 95.1 – 183.8) indicated for a flavone backbone. Thus, the AX aromatic coupled proton signals were assigned for H-6 and H-8 of the A-ring of flavone and the ABX aromatic coupled protons were assigned for three protons in the B-ring of flavone. Another singlet olefinic proton was assigned for H-3 (δ_H 6.62). An anomeric carbon (δ_C 103.2) and five carbinol carbons (δ_C 74.8, 77.6, 71.3, 78.5, 62.4) suggested the presence of glucopyranosyl group. Additionally, a coupling constant value of anomeric proton (δ_H 4.96, *J* = 7.8 Hz) indicated for *β*-glucopyranosyl linkage. Location of the glucopyranosyl group was determined at C-4′ by HMBC correlation between anomeric proton (δ_H 4.96)/ H-2′ (δ_H 7.45)/ H-6′ (δ_H 7.17) and C-4′ (δ_C 150.0). Consequently, compound **2** was determined to be luteolin 4′-O-glucopyranoside [15].

The ^{1}H-NMR spectrum of compound **3** showed signals of eight deshielded protons including four protons of the AA′BB′ coupled system [δ_H 7.92 (2H, d, *J* = 8.0 Hz) and 6.90 (2H, d, *J* = 8.0 Hz)], two meta coupled protons [δ_H 6.19 (1H, d, *J* = 2.0 Hz) and 6.48

(1H, d, *J* = 2.0 Hz)], a olefinic proton [δ_H 6.78 (1H, s], and an ultrahydrogen bonding hydroxy group [δ_H 12.90 (1H, s]. The ^{13}C-NMR spectrum of **3** showed signal of 15 sp^2 hybridized carbons, indicating a flavone backbone. Therefore, the AA′BB′ coupled protons system indicated for B-ring of flavone. The meta coupled protons were assigned for H-6 and H-8. A singlet olefinic proton (δ_H 6.78) was assigned for H-3 and ultrahydrogen bonding hydroxy signal was assigned for 5-OH. Thus, compound **3** is determined to be 5,7,4′-trihydroxyflavone, a popular flavonoid known as apigenin [16].

The ^{1}H and ^{13}C-NMR spectra of **4** showed closely similar with those of **3** by signals of apigenin flavone frame-work. The NMR spectral data of **4** exhibited additional signals of sugar moiety.

TABLE II. ^{1}H- AND ^{13}C-NMR SPECTROSCOPIC DATA OF COMPOUNDS **5** – **6**

No.	[e)]**4**		[f)]**5**		[f)]**6**	
	[a]δ_C	[b]δ_H (mult., *J* in Hz)	[a]δ_C	[b]δ_H (mult., *J* in Hz)	[a]δ_C	[b]δ_H (mult., *J* in Hz)
2	163.5	-	158.6	-	158.6	-
3	103.7	6.86 s	135.7	-	136.0	-
4	182.6	-	179.3	-	179.3	-
5	161.9	-	162.9	-	162.9	-
6	100.1	6.45 (s)	100.0	6.21 (1.8)	99.9	6.17 (br s)
7	165.0	-	166.4	-	166.1	-
8	95.4	6.77 (s)	94.7	6.39 (1.8)	94.6	6.35 (br s)
9	157.6	-	158.4	-	158.3	-
10	105.9	-	105.5	-	105.6	-
1′	121.6	-	121.7	-	121.7	-
2′	129.2	7.95 (d, 8.0)	109.8	7.32 (s)	109.9	7.39 (s)
3′	116.6	6.96 (d, 8.0)	146.4	-	146.3	-
4′	157.6	-	138.1	-	138.1	-
5′	116.6	6.96 (d, 8.0)	146.4		146.3	-
6′	129.2	7.95 (d, 8.0)	109.8	7.32 (s)	109.9	7.39 (s)
1″	101.1	5.06 (d, 7.2)	104.8	5.18 (d, 7.2)	105.5	5.18 (d, 7.8)
2″	73.5	3.11-3.47 (m)	72.9	3.92 (dd, 9.0, 7.2)	73.3	3.86 (dd, 7.8, 8.5)
3″	76.7	3.11-3.47 (m)	74.2	3.89 (br d, 9.0)	75.1	3.63 (br d, 8.5)
4″	71.2	3.11-3.47 (m)	69.2	3.86 (br s)	70.1	3.90 (br s)
5″	76.1	3.11-3.47 (m)	67.0	3.50 (dd, 12.0, 1.2) 3.68 (dd, 12.0, 3.0)	77.2	3.55 (m)
6″	66.6	3.85 (br d, 11.2) 3.60 (m)			61.9	3.67 (dd, 6.0, 11.0) 3.61 (m)
1‴	100.4	4.55 (br s)				
2‴	70.7	3.65 (br s)				
3‴	70.0	3.11-3.47 (m)				
4‴	72.5	3.11-3.47 (m)				
5‴	68.8	3.11-3.47 (m)				
6‴	18.2	1.07 (d, 6.0)				

Measured at [a)]100 MHz, [b)]400 MHz, [c)]150 MHz, [d)]600 MHz, [e)]DMSO-d_6, [f)]CD_3OD.

The presence of two anomeric protons [δ_H 5.06 (1H, d, *J* = 7.2 Hz) and 4.55 (1H, br s)] indicated for a disaccharide. Moreover, a broad singlet anomeric proton (δ_H 4.55) and a doublet methyl group [δ_H 1.07 (3H, d, *J* = 6.0 Hz)] suggested the presence of rhamnopyranosyl group. Other monosaccharide was determined to be glucose by six carbinol signals (δ_C 101.1, 73.5, 76.7, 71.2, and 66.6). The downfield shifted chemical shift value of Glc C-6″ (δ_C 66.6) suggested for rhamnopyranosyl-(1→6)-glucopyranose disaccharide, an abundant naturally occuring disaccharide known as rutinose. Additionaly, the coupling constant value of anomeric proton of glucose (δ_H 5.06, *J* = 7.2 Hz) suggested for a *β*-rutinosyl linkage. Thus, compound **4** was determined to be apigenin 7-*O*-*β*-rutinoside [17].

Compound **5** was isolated as a pale yellow amorphous powder. The ^{1}H-NMR spectrum of **5** contained proton signals corresponding for two *meta*-coupled aromatic protons [δ_H 6.21 (1H, d, *J* = 1.8 Hz) and 6.39 (1H, d, *J* = 1.8 Hz)], a pair of magnetic equivalent aromatic protons [δ_H 7.32 (2H, s)], and an anomeric proton [δ_H 5.18 (1H, d, *J* = 7.2 Hz)]. The ^{13}C-NMR spectrum of **5** showed signal of 20 carbons, including 15 carbons of a flavone backbone and five carbon of a pentose. Similar with compounds **2**–**4**, the two *meta*-coupled aromatic protons (δ_H 6.21 and 6.39) were assigned for H-6 and H-8 of the flavone backbone. A pair of magnetic equivalent aromatic protons (δ_H 7.32), therefore, indicated symetric structural fragment of the B-ring, normal suggesting for 3′,4′,5′-trihydroxy substitutions. This deduction is consisted with chemical shift values of C-3′ (δ_C 146.4), C-4′ (δ_C 138.1), and C-5′ (δ_C 146.4). The structure of pentose moiety was deduced as arabinopyranose which confirmed by its carbon chemical shitf values (δ_C 104.8, 72.9, 74.2, 69.2, and 67.0) and a broad signlet of proton signal H-4″ [δ_H 3.86 (br s)]. The glycosidic linkage was confirmed to be *α*-arabinopyranoside by coupling constant value of anomeric proton (δ_H 5.18, *J*

= 7.2 Hz). Therefore, compound **5** is determined to be 6,8,3′,4′,5′-pentahydroxyflavone 3-*O*-*α*-arabinopyranoside, an abunant flavone glycoside known as myricetin 3-*O*-*α*-arabinopyranoside [18, 19].

Compound **6** was isolated as a pale yellow amorphous powder. The ^{1}H and ^{13}C-NMR spectral data of **6** closely resembled with those of **5**, except signals of sugar moiety. The aglycone of these two compounds therefore were identical, 3,6,8,3′,4′,5′-hexahydroxyflavone. Meanwhile, six carbinol carbons (δ_C 105.5, 73.3, 75.1, 70.1, 77.2, and 61.9) and a broad singlet of H-4″ [δ_H 3.90 (br s)] indicated the presence of galactopyranosyl group. Additionally, the coupling constant value of anomeric proton (δ_H 5.18, *J* = 7.8 Hz) indicated a *β*-galactopyranosyl linkage. Thus, compound 6 is determined to be 6,8,3′,4′,5′-pentahydroxyflavone 3-*O*-*β*-galactopyranoside, an abunant flavone glycoside known as myricetin 3-*O*-*β*-galactopyranoside [20, 21].

The leaves and twigs of *P. frutescens* have been traditionally used to reduce uric acid level [14]. Therefore, compounds **1**–**6** were evaluated for their *in vitro* xanthine oxidase inhibitory activity, a crucial enzyme in regulation the formation of uric acid. Compounds **1**–**6** exhibited xanthine oxidase inhibitory activity with IC_{50} values of 8.3 ± 0.7, 11.5 ± 0.4, 47.0 ± 2.2, 26.6 ± 1.5, 18.2 ± 0.9, and 15.7 ± 1.1 µM in comparison with positive control, allopurinol (IC_{50} value of 3.0 ± 0.4 µM). These results indicated that phenolic components from *P. frutescens* could be active ingredients for xanthine oxidase inhibitory activity.

In summary, six phenolic components including (*R*)-rosmarinic acid, luteolin 4′-*O*-*β*-glucopyranoside, apigenin, apigenin 7-*O*-*β*-rutinoside, myricetin 3-*O*-*α*-arabinopyranoside, and myricetin 3-*O*-*β*-galactopyranoside were isolated from the leaves and twigs of *P. frutescens*. These compounds exhibited xanthine oxidase inhibitory activity with IC_{50} values ranging of 8.3 – 47.0 µM. The results indicated that phenolic components could be active ingredients of the *P. frutescens* for its property in reducing uric acid level.

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