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Structural Elucidation of Some Phenolic Compounds from the Leaves of *Kadsura Coccinea* in Vietnam

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Abstract

*Natural products and their derivatives represent more than 50% of all the drugs in modern therapeutics. Flavonoids and lignans are a large group of naturally occurring and play a variety of biological activities in plants. Schisandraceae family includes 2 genera, Schisandra and Kadsura with about 39 species of plants. The Kadsura coccinea, belonging to Schisandraceae family, is mainly distributed in the tropical and subtropical regions of South and Southeast Asia. The aim of this study is the isolation and structural elucidation of compounds isolated from the leaves of Kadsura coccinea. For this purpose, five known flavonoid compounds, (+) gallocatechin (**1**), catechin (**2**), (-) epicatechin (**3**), phloretin-2-O-glucoside (**4**), phloretin-4-O-glucoside (**5**) together with 2-hydroxy-5-methoxyphenyl-O-β-D-glucopyranoside (**6**) and icariside E3 (**7**) were isolated. Their structures are elucidated by NMR spectroscopic analysis as well as compared with the literature. Especially, compound **6** is the first isolated from this plant.*

Keywords: *Kadsura coccinea*, Schisandraceae, flavonoid, phenolic.

1. Introduction

Schisandraceae family includes two genera, *Schisandra* and *Kadsura* with about 39 species of plants. Schisandraceae are woody vines, monoecious or dioecious. Leaves alternate or clustered, exstipulate, petiolate, lamina simple. Flowers generally solitary and axillary to leaves on ultimate branches, or in axils of fugacious bracts near base of ultimate shoots. They occasionally in pairs or in clusters of up to 8, unisexual, hypogynous, few to numerous parts generally spirally arranged, pedicellate [1].

Kadsura coccinea (Lem.) A. C. Smith (commoly known as *Kadsura coccinea*) with Vietnamese name: na rừng, nắm cơm, dây xưn xe, ngũ vị nam belong to Schisandraceae family, a climbing plant distributed in the tropical and subtropical regions of South and Southeast Asia, China, Japan, Laos, Cambodia, Thailand, Myanmar, Sri Lanka... In Vietnam, it is found in Lao Cai, Yen Bai, Thai Nguyen, Lang Son, Vinh Phuc, Ha Noi, Quang Tri, Kon Tum, Lam Dong.

K. coccinea is large vines with slithered branches, leaves are oval or oblong, 6-10 cm long, 3-4 cm wide, very smooth. The stems of *K. coccinea* have a sour, sweet taste, warmth, and they are used in traditional medicine for stimulate digestion, relieve pain [2].

In previous investigations on the stems, rhizomes, roots and fruits of *K. coccinea,* lignans, terpenoids, steroids and phenolic compounds were reported. So far 202 different compounds have been isolated from this plant. The chemical constituents of this plant have been reported with several different bioactivities, including anti-HIV, anti-tumour, cytotoxic, anti-inflammatory, anti-hepatitis, nitric oxide inhibitory, anti-platelet aggregation, and neuroprotective effects [1,3].

K. coccinea is a rich source of lignans and its derivatives. According to skeleton types, *K. coccinea* lignans can be divided into four categories, including dibenzocloctadiene, spirobenzofuranoid dibenzocyclooctadienes, diarylbutanes and arylnaphthalene lignans with 79 compounds [3].

A small number of flavonoids isolated from *Kadsura coccinea* have been published. According to the study of Han Dong-Sun *et al*., in 2012, one flavonoid isolated from this plant is ascovertin [4].

Genus *Kadsura* is famous for the presence of structurally diverse triterpenoids. Many of these important triterpenoids are the first time reported from *K. coccinea*. These also included several highly oxygenated triterpenoids with different skeletons. In recent years, a series of nortriterpenoids and kadlongilactones with novel structures have also been isolated and identified from this plant These reported triterpenoids mainly belong to intact lanostanes, seco-lanostanes, intact cycloartanes, and seco-cycloartanes types [3].

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In Vietnam, there were researches about chemical constituents of this plant. Ninh Khac Ban *et al*. isolated four dibenzocyclooctadiene lignans and two lanostane-type-tritepenes from the roots of *Kadsura coccinea* in 2009 [5]. In a research of Tran Manh Hung *et al*., there were five lanostane-triterpenes from the leaves of this plant with cytotoxic effect against PANC-1 have been reported [6].

In this study, five known flavonoids (+)- gallocatechin (**1**), catechin (**2**), (-) epicatechin (**3**), phloretin-2-*O*-glucoside (**4**), phloretin-4-*O*-glucoside (**5**) together with two known phenolics 2-hydroxy-5-methoxyphenyl-*O*-*β*-D-glucopyranoside (**6**) and icariside E3 (**7**) were isolated. This paper reports the isolation and the structural elucidation of these compounds.

2. Experiments

2.1. Plant Materials

The leaves of *K. coccinea* were collected in May 2017 from Tam Dao, Vinh Phuc province, Vietnam. The identification of the plant was performed by Professor Tran Huy Thai, Institute of Ecology and Biological Resources, VAST, Vietnam. A voucher specimen (KC–201705) was deposited at the Herbarium of School of Chemical Engineering, Hanoi University of Science and Technology, Vietnam.

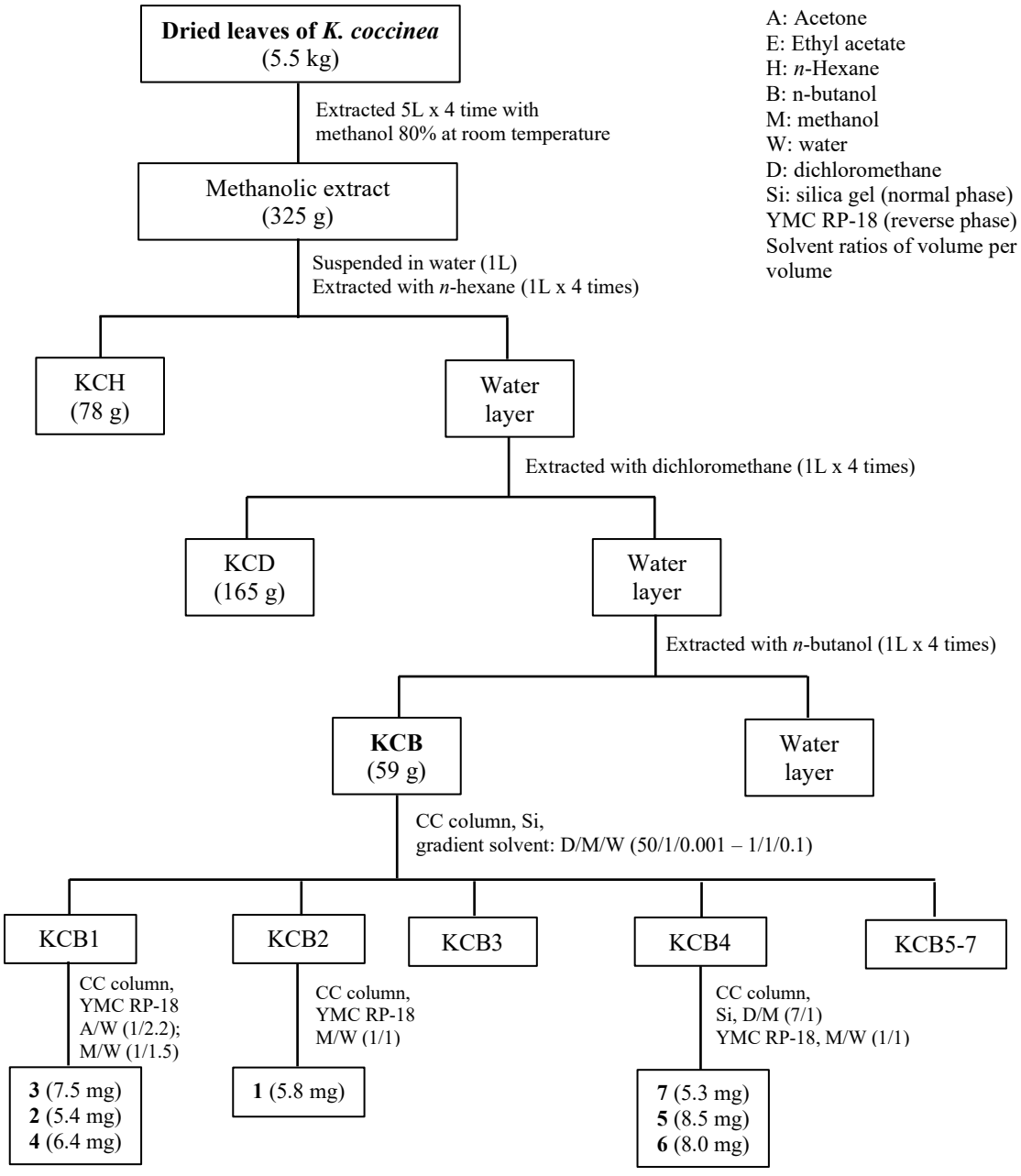

Fig. 1. Isolation scheme of *Kadsura coccinea* leaves.

After removing dust and other matter, the leaves of *K. coccinea* were chopped, dried under shiny light, and oven-dried at 50 ^{o}C to give dried samples.

2.2 General Experimental Procedures

The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded. The NMR spectra of isolates (**1**–**7**) were recorded on a *J*EOL *J*NM-AL 400 MHz spectrometer, and chemical shifts were expressed as δ values (ppm) with TMS as internal standard (measured in pyridine-d_5). Column chromatography (CC) was performed on silica gel (Kieselgel 60, 70–230 mesh and 230-400 mesh, Merck), porous polymer gel (Diaion® HP-20, 20–60 mesh, Mitsubishi Chemical, Tokyo, *J*apan), Sephadex™ LH-20 (GE Healthcare Bio-Sciences AB, Uppsala, Sweden), and YMC RP-18 resins (30–50 µm, Fu*J*i Silysia Chemical). Thin layer chromatography (TLC) used pre-coated silica gel 60 F_{254} (1.05554.0001, Merck) and RP-18 F_{254S} plates (1.15685.0001, Merck) and compounds were visualized by spraying with aqueous 10% H_2SO_4 and heating for 1.5-2 min.

2.3. Extraction and Isolation

The dried leaves of *K. coccinea* (5.5 kg) were extracted with 80% methanol (5L × 4 times) at room temperature for 48 h. The MeOH extract was then dried under reduced pressure (325 g). The concentrated MeOH extract was suspended in H_2O (1.0L) and partitioned successively with *n*-hexane (1L × 4 times, 78 g), CH_2Cl_2 (1L × 4 times, 165 g), n-butanol (1L × 4 times, 59 g) and H_2O-layer. The *n*-butanol fraction (59 g) was separated on a silica gel column chromatography eluting with CH_2Cl_2/MeOH/H_2O (from 50/1/0.001-1/1/0.1) to obtain seven sub-fractions (KCB1–KCB7) according to their TLC profiles. Sub-fraction KCB1 (7.5 g) was chromatographed on an YMC RP-18 chromatography eluting with acetone/H_2O (1/2.2, v/v) and MeOH/H_2O (1/1.5, v/v) to give **2** (5.4 mg), **3** (7.5 mg) and **4** (6.4 mg). Sub-fraction KCB2 (550 mg) was sub*J*ected to YMC RP-18 chromatography, eluting with MeOH/H_2O (1/1, v/v) to afford **1** (5.8 mg). Sub-fraction KCB4 (0.86g) was separated on silica gel column chromatography eluting with CH_2Cl_2/MeOH (7/1, v/v) effort compound **6** (8.0 mg). This sub-fraction was further purified by YMC RP-18 chromatography, eluting with acetone/H_2O (1/2, v/v) to give **7** (5.3 mg) and **5** (8.5 mg) (see Fig. 1).

Table 1. ^{1}H-NMR (400 MHz, methanol-d_4) and ^{13}C-NMR (100 MHz, methanol-d_4) data of **1, 2** and **3**

Position	Compound 1		Compound 2		Compound 3	
	δ_C	δ_H mult. (*J* in Hz)	δ_C	δ_H mult. (*J* in Hz)	δ_C	δ_H mult. (*J* in Hz)
1	-	-	-	-	-	-
2	82.8	4.5, d (7.2)	82.7	4.55, d, 7.8	79.9	4.83, brs
3	68.7	3.99, m	68.7	3.98, ddd, 8.4, 7.8, 5.5	67.8	4.19, s
4	28.1	2.53, dd (16.8,7.5)	28.4	2.55, dd, 16.1, 8.4	29.3	2.85, d, 17.0
5	156.8	-	157.6	-	158.0	-
6	95.5	5.87, brs	96.2	5.91, s	96.4	5.96, d, 1.8
7	157.6	-	157.7	-	157.7	-
8	96.2	5.86, brs	95.5	5.84, s	95.9	5.93, d, 1.8
9	156.8	-	156.8	-	157.4	-
10	100.7	-	100.8	-	100.1	-
1'	134.5	-	132.1	-	132.3	-
2'	107.2	6.4, brs	115.2	6.82, d, 1.9	115.3	6.99, d, 1.8
3'	146.8	-	146.1	-	145.9	-
4'	134	-	146.2	-	145.8	-
5'	146.8	-	116.1	6.74, d, 8.1	115.9	6.76, d, 8.0
6'	107.2	6.4, brs	120.0	6.69, d, 1.9	119.4	6.8, dd, 8.0, 1.8

(+) Gallocatechin (**1**)

A yellow powder; α_D^{25} +15.3, ESI-MS *m/z*: 307 $[M + H]^+$, molecular formula of $C_{15}H_{14}O_7$; ^{1}H-NMR (400 MHz, methanol-d_4) and ^{13}C-NMR (100 MHz, methanol-d_4) data (see *Table 1*)

Catechin (**2**)

A yellow powder; ESI-MS *m/z*: 291 $[M + H]^+$, molecular formula of $C_{15}H_{14}O_6$; ^{1}H-NMR (400 MHz, methanol-d_4) and ^{13}C-NMR (100 MHz, methanol-d_4) data (see *Table 1*).

(-) Epicatechin (**3**)

A yellow powder; α_D^{25} -58.2, ESI-MS *m/z*: 291 $[M + H]^+$, molecular formula of $C_{15}H_{14}O_6$; ^{1}H-NMR (400 MHz, methanol-d_4) and ^{13}C-NMR (100 MHz, methanol-d_4) data (see *Table 1*).

Phloretin-2-O-glucoside (**4**)

A red-yellow powder; ESI-MS *m/z*: 435 $[M + H]^+$, molecular formula of $C_{21}H_{24}O_{10}$; ^{1}H-NMR (400 MHz, methanol-d_4): δ 7.07 (m, 2H), 6.69 (m, 2H), 6.18 (d, J = 2.0 Hz, 1H), 5.95 (d, J = 2.2 Hz, 1H), 5.04 (d, J = 7.4 Hz, 1H), 3.89 (dd, J = 12.2, 2.3 Hz, 1H), 3.47 (dd, J = 12.2, 5.6 Hz, 1H), 3.46 (dd, J = 9.3, 7.4 Hz, 1H), 3.45 (t, J = 9.3 Hz, 1H), 3.43 (m, 2H), 3.47 – 3.43 (m, 1H), 3.31 (t, J = 9.1 Hz, 1H), 2.87 (dtd, J = 11.5, 7.1, 6.7, 4.4 Hz, 2H) and ^{13}C-NMR (100 MHz, methanol-d_4): δ 206.5, 167.5, 165.9, 162.3, 156.3, 133.9, 130.4, 116.1, 106.8, 102.1, 98.3, 95.4, 78.5, 78.4, 74.7, 71.1, 62.4, 47.0, 30.8.

Table 2. ^{1}H-NMR (400 MHz, methanol-d_4) and ^{13}C-NMR (100 MHz, methanol-d_4) of compound **6** and **7**

Position	Compound 6		Compound 7	
	δ_H mult. (J in Hz)	δ_C	δ_H mult. (J in Hz)	δ_C
1	-	142.9	-	140.3
2	-	117.9	6.72 brs	111.7
3	7.58 d (2.2)	149.2	-	143.6
4	6.52 d (8.5)	152.8	-	153.1
5	-	117.7	-	138.5
6	7.41 dd (2.2, 8.5)	126.1	6.72 brs	120.3
7	-	-	2.63 t (6.5)	33.1
8	-	-	1.81 m	35.5
9	-	-	3.56 t (6.4)	62.2
1'	4.6 d (7.26)	102.9	-	133.3
2'	3.3-3.7 m	73.1	6.56 d (8.1)	113.0
3'	-	75.9	-	145.3
4'	-	69.5	-	148.4
5'	-	76.4	6.47 d (1.7)	115.6
6'	3.3-3.7 m	60.7	6.56 dd (1.7, 8.1)	122.6
7'	-	-	2.97 dd (5.1, 13.6)	39.2
8'	-	-	3.95 m	42.7
9'	-	-	3.76 m	67.1
OCH_3	3.69 s	-	3.68 s	56.2
1"	-	-	4.60 d (7.3)	56.3
2"	-	-	3.42 m	105.6
3"	-	-	3.38 m	78.0
4"	-	-	3.12 m	71.2
5"	-	-	3.63 m	77.8
6"	-	-	3.76 m	62.5

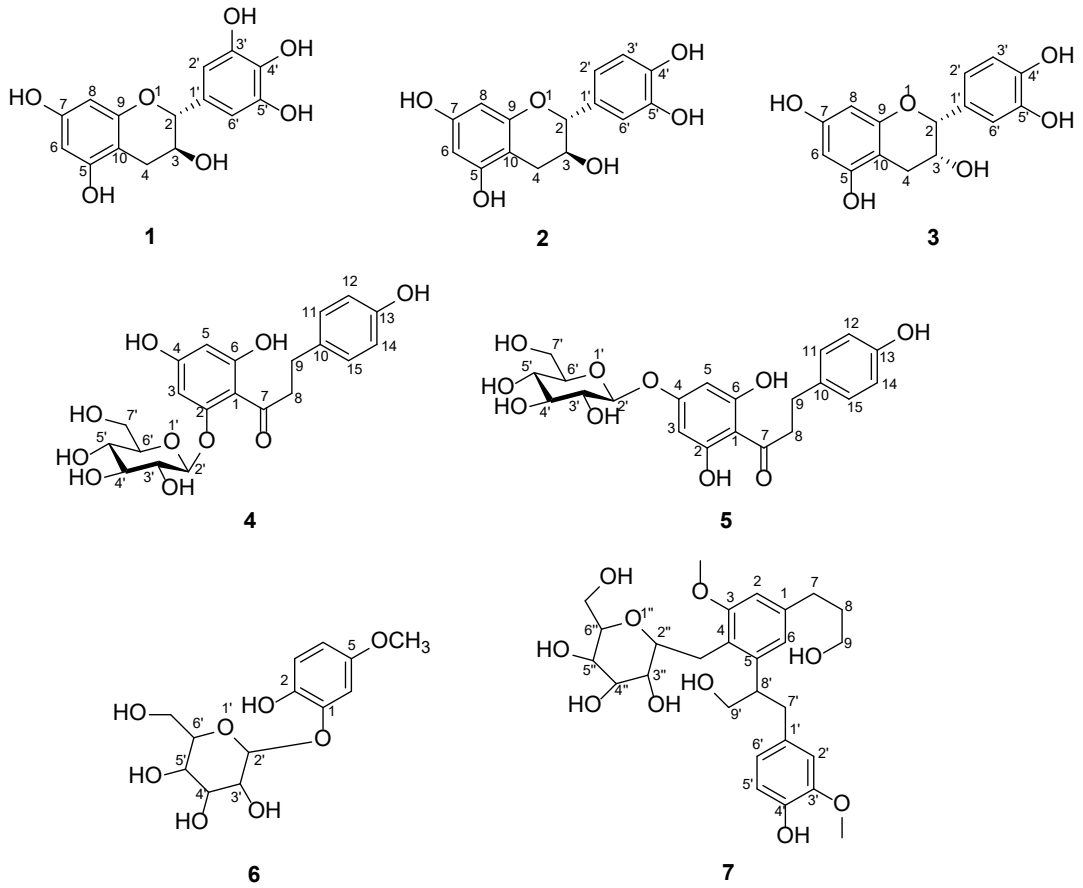

Fig. 2. Structure of isolated compounds.

Phloretin-4-O-glucoside (**5**)

A pale-yellow powder; ESI-MS *m/z*: 435 [M + H]$^+$, molecular formula of $C_{21}H_{24}O_{10}$; ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.95 – 6.91 (m, 2H), 6.59 (d, J = 8.4 Hz, 2H), 5.99 (d, J = 1.7 Hz, 2H), 4.83 (dd, J = 7.6, 1.6 Hz, 1H), 3.81 (dd, J = 12.2, 2.3 Hz, 1H), 3.62 (dd, J = 160 12.2, 5.5 Hz, 1H), 3.37 (t, J = 9.3 Hz, 1H), 3.36 (t, J = 9.3 Hz, 1H), 3.35 (dd, J = 9.3, 7.5 Hz, 1H), 3.30 (t, J = 9.2 Hz, 1H), 3.19 (dd, J = 8.8, 7.0 Hz, 2H), 2.75 (t, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, methanol-d_4) δ 207.13, 165.06, 164.85, 156.51, 133.96, 130.43, 116.23, 166 106.99, 101.21, 96.55, 78.34, 77.99, 74.73, 71.25, 62.49, 47.61, 31.31.

2-hydroxy-5-methoxyphenyl-O-β-D-glucopyranoside (**6**)

A yellow sticky deposit; ESI-MS *m/z*: 302 [M + H]$^+$, molecular formula of $C_{13}H_{18}O_8$; ^{1}H-NMR (400 MHz, methanol-d_4) and ^{13}C-NMR (100 MHz, methanol-d_4) data (see *Table 2*).

Icariside E3 (**7**)

A colorless powder; ESI-MS *m/z*: 548 [M + H+ Na]$^+$, molecular formula of $C_{15}H_{14}O_6$; ^{1}H-NMR (400 MHz, methanol-d_4) and ^{13}C-NMR (100 MHz, methanol-d_4) data (see *Table 2*). The structure of isolated compounds are shown in Fig. 2.

3. Results and Discussion

Compound **1** was obtained as a yellow powder. In the ^{1}H NMR spectrum, compound **1** showed two aromatic protons resonated a proton signal at δ_H 6.40 (2H, brs), which were assigned to H-2' and 6', respectively, and meta coupling proton at δ_H 5.87 and 5.86 (each, 1H, brs) assigned to H-6 and H-8, respectively. The ^{13}C-NMR spectrum displayed significant signals of three hydroxy carbon substitutions at δ_C 146.8 (C-3', 5') and at δ_C 134.0 (C-4') in ring C. Two hydroxy methine carbons at δ_C 82.8 (C-2) and δ_C 68.7 (C-3) together with a methylene carbon at δ_C 28.1 (C-4) were also observed. After detailed comparison of the ^{1}H and ^{13}C NMR with those published in compound **1** was identified as (+) gallocatechin (**1**) [4].

Compound **2** was obtained as a yellow powder. In the ^{1}H NMR spectrum, compound **2** showed an ABX spin system at δ_H 6.82 (1H, d, J = 1.8 Hz, H-2'), 6.74 (1H, d, J = 8.1 Hz, H-5'), 6.69 (1H, dd, J = 8.1, 1.8 Hz, H-6'), and meta coupling protons at δ_H 5.91 and 5.84 (each 1H, s) assigned to H-6 and H-8,

respectively. The ^{13}C NMR spectrum displayed significant signals of two hydroxy carbon substitutions at δ_C 146.1 (C-3') and at δ_C 146.2 (C-4') in ring C. Two hydroxy methine carbons at δ_C 82.7 (C-2) and δ_C 68.7 (C-3) together with a methylene carbon at δ_C 28.4 (C-4) were also observed. ^1H and ^{13}C NMR of compound **2** were compared to those which was identified as catechin [7].

Compound **3** was obtained as a yellow powder. In the ^1H and ^{13}C NMR spectra of compound **3** were consisted to similar to those of **2** except for differences from two methine hydroxyl groups shifted downfield to respects of **2** at δ_C 79.9 (C-2) and 67.8 (C-3). Furthermore, the small value of H-2 (δ_H 4.83, 1H, brs) suggested the same side of planar for H-2 and H-3. Thus, the spectroscopic data of **3** was consistent with that of literature and identified as (-) epicatechin [7].

Compound **1, 2, 3** were isolated in many plants and exhibited antioxidant activity [7].

Compound **4** was obtained as a red-yellow powder. In the ^1H NMR spectrum, compound **4** showed the *ortho*-coupled A_2B_2-type aromatic proton at δ_H 7.07 and 6.69 (each 2H, d, J = 8.3 Hz) assigned to H-11, 15 and H-12, 14, respectively, and meta coupling proton at δ_H 6.18 and 5.96 (each 1H, d, J = 2.1Hz) assigned to H-2 and H-6, respectively. The ^{13}C NMR spectrum displayed a carboxyl group at δ_C 206.5 (C-7), four oxygenated olefin quaternary carbon signals at δ_C 167.5 (C-5), 165.9 (C-1), 162.3 (C-3), and 156.3 (C-13). After detailed comparison of the ^1H and ^{13}C NMR with those published in literature, compound **4** was identified as phloretin-2-*O*-glucoside [8].

Compound **5** was obtained as a pale-yellow powder. In the ^1H NMR spectrum, compound **5** showed the *ortho*-coupled A_2B_2-type aromatic proton at δ_H 6.95 and 6.59 (each 2H, d, J = 8.3 Hz) assigned to H-11, 15 and H-12, 14, respectively, and meta coupling proton at δ_H 5.99 (d, J = 2.1 Hz, 2H) assigned to H-2 and H-6, respectively. The ^{13}C NMR spectrum displayed a carboxyl group at δ_C 207.13 (C-7), four oxygenated olefin quaternary carbon signals at δ_C 165.06 (C-5), 164.85 (C-1), 156.51 (C-3), and 133.96 (C-13). The different between compound **5** and compound **4** is the glucoside moiety at C-2 position in **4** is replaced by the glucoside moiety at C-4 position in **5.** By comparison with literature, compound **5** was identified as phloretin-4-*O*-glucoside [9].

Phloretin is a dihydrochalcone, an intermediate of the biosynthetic pathway of flavonoids in plants, which is abundantly present in the peel of apple and in strawberries. They occur in different glycosidic forms, such as naringin dihydrochalcone, phlorizin, and phloretin-4-*O*-glucoside, in the different parts of the plants, contributing to various physiological properties of the plants, as well as to their color. Phloretin and its glycosides have been determined to have beneficial biological activities. Studies have uncovered that phloretin has inhibitory activity against glucose cotransporter, antioxidant activity. It also has activity to suppress the tumor necrosis factor alpha-induced inflammatory response, ameliorate inflammation of the colon, positively affect body weight loss, modulate Ca^{2+}-activated K^+ channels, and increase endothelial nitric oxide production, which might help to protect against atherosclerosis. Importantly, phloretin has other biological functions, like anticarcinogenic and estrogenic activities and inhibition of cardiovascular disease [9].

Compound **6** was collected as a yellow sticky deposit. ^1H NMR spectrum of **6** showed the presence of an ABX spin system [δ_H 6.75 (d, J = 2.6 Hz), 6.64 (d, J = 8.6 Hz), and 6.53 (dd, J = 2.6, 8.6 Hz)], and anomeric proton at δ_H 4.69 (d, J = 6.8 Hz), and methoxy group at δ_H 3.78. The location of methoxy group as well as the position of glucosylation were detected by extensive study of HMBC experiment (see Fig. 3).

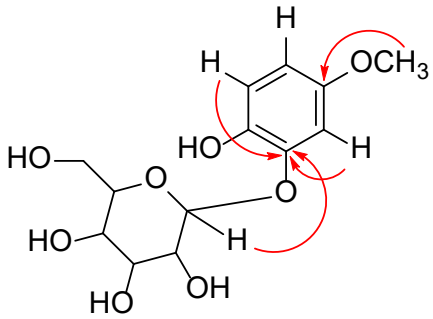

Fig. 3. HMBC relations of compound **6**.

The HMBC spectrum showed the correlations of H-3 (δ_C 6.64)/ H-6 (δ_C 6.75)/H-1' (δ_H 4.69) to C-1 (δ_C 152.8) and those of methoxy group at δ_H 3.78 to C-5 (δ_C 149.2), allow to establish the structure of **6** as 2-hydroxy-5-methoxyphenyl β-D-glucopyranoside. This is the first report of 2-hydroxy-5-methoxyphenyl β-D-glucopyranoside from this plant [10,11].

Compound **7** was obtained as a colorless powder. The ^1H NMR spectrum of **7** showed the significant signals of two *meta*-coupling doublets at δ_H 6.72 (2H, brs, H-2, 6) and an ABX spin system [δ_H 6.56 (2H, m, H-2', 6') and 6.47 (1H, d, J = 8.1 Hz, H-5')], respectively. Addition, the presence of an anomeric proton at δ_H 4.61 (1H, d, J = 7.3 Hz) suggested the presence of an β-glycoside, two methoxy protons [δ_H 3.80 (3H, s) and 3.70 (3H, s)], and two methylene protons at δ_H 1.81 (2H, m, H-7).

The ^{13}C NMR spectrum of **7** showed the presence of 18 carbons of skeleton at δ_C 153.1 (C-5), 148.4 (C-3'), 145.3 (C-4'), 143.6 (C-4), 140.3 (C-1), 138.5 (C-3), 133.3 (C-1'), 122.6 (C-6'), 120.3 (C-2), 115.6 (C-5'), 113.6 (C-2'), 111.7 (C-2), 67.1 (C-9'), 62.5 (C-

9), 42.8 (C-8'), 39.2 (C-7'), 35.6 (C-8), and 33.1 (C-7). The carbon signal at δ_C 104.6 (C-1"), 78.1 (C-3"), 77.9 (C-5"), 75.9 (C-2"), 71.2 (C-4"), and 62.2 (C-6") suggested that the structure of **7** contained a glucoside moiety. Based on the above evidence and comparison with the literature data, compound **7** was identified as icariside E_3. This compound was previously isolated from *Epimedium grandiflorum* and *Ulmus davidiana* var *Japonica* [12].

4. Conclusion

By modern methods of isolation and spectroscopy, we isolated and determined the structure of 7 compounds from the leaves of *Kadsura coccinea* in Vietnam. Five known flavonoid compounds, (+) gallocatechin (**1**), catechin (**2**), (-) epicatechin (**3**), phloretin-2-*O*-glucoside (**4**), phloretin-4-*O*-glucoside (**5**) together with 2-hydroxy-5-methoxyphenyl-*O*-*β*-D-glucopyranoside (**6**) and icariside E3 (**7**) were isolated. The spectral data of them were in agreement with the literature data. These compounds were previously isolated from many different plants. Interestingly, compound **6** was isolated for the first time from *K. coccinea*. This study demonstrates that *K. coccinea* is a useful source for the provision of phenolic compounds. Furthermore, our study is the groundwork for further studies in searching for interesting structurally active substances from nature.

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