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FLAVONOIDS FROM *KNEMA SQUAMULOSA* W.J. DE WILD. AND THEIR ANTIMICROBIAL ACTIVITY

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Summary

Flavonoids from *Knema squamulosa* W.J. de Wild. and their Antimicrobial Activity

Using chromatographic separation methods, seven compounds were isolated from the methanolic extract of the twigs and leaves of *Knema squamulose* W.J.de Wild. Their structures were elucidated as: sulfuretin (**1**), (-)-3,4',7-trihydroxy-3'-methoxyflavan (**2**), 7-hydroxy-3',4'-methylenedioxyflavan (**3**), (-)-liquiritigenin (**4**), eriodictyol (**5**), chysoeriol (**6**), and luteolin (**7**) using 1D and 2D-NMR experiments and comparison to those reported in the literature. All the isolated compounds were evaluated for their inhibitory activity against several bacterial and yeast strains.

Keywords: *Knema squamulosa,* Myristicaceae, *Flavonoids, Antimicrobial activity.*

1. Introduction

The genus *Knema* (Myristicaceae) contains over 60 species that are distributed in tropical and subtropical regions of Asia and Pacific islands [1]. Plants in the *Knema* genus have been used in the Asian traditional medicine for the treatment of diseases pertaining to skin or mouth and throat sores [1]. There are about 14 species are found in Vietnam and *Knema squamulosa* W.J. de Wild. belonging to the genus *Knema*, is an endemic plant in Vietnam [2],[3]. To date, some secondary metabolites have been reported from *Knema* species, including alkyl phenols and alkylphenyl phenols, lignans, acetophenones, and flavonoids [4],[5]. *Knema* plants have exhibited diverse pharmacological effects such as antibacterial, anti-inflammatory, antioxidant, cytotoxic, neuroprotective, and acetylcholinesterase inhibitory activities [6],[7]. As a part of our investigations of the chemical constituents and biological activities of Vietnamese medicinal plants [8],[9], we report herein the isolation and structural elucidation of seven compounds from the twigs and leaves of *K. squamulosa*. To the best of our knowledge, this is the first report on the chemical constituents of *K. squamulosa*.

2. Material and methods

2.1. General experimental procedures

All solvents and reagents were of analytical grade and were used as received without further purification. Optical rotations were measured at room temperature on a JASCO P-2000 polarimeter (Tokyo, Japan). The circular dichroism (CD) spectrum was recorded on a Chirascan circular dichroism spectrometer (Applied Photophysics, UK). The NMR data were recorded on Bruker AVANCE NEO 600 FTNMR spectrometers (Brucker, Gemany). Column chromatography (CC) was carried out on *silica gel* (Kieselgel 60, 70-230 mesh and 230-400 mesh, Merck, Darmstadt, Germany), YMC*GEL (ODS-A, 12 nm S-150 mm, YMC). Thin-layer chromatography (TLC) was performed on Merck precoated *silica gel* 60 F_{254} (1.05554.0001) and RP-C_{18} F_{254S} plates (1.15685.0001). TLC spots were detected under UV light (254 and 365 nm) and visualized by spraying with H_2SO_4 10% (v/v) aqueous solution.

2.2. Plant material

The samples of *K. squamulosa* were collected at Gia Lai, Kon Tum province, Vietnam, in March 2019, and identified by Dr. Nguyen The Cuong (Institute of Ecology and Biological Resources, VAST, Vietnam). A voucher specimen (KHCBHH-T.02) was deposited at the Institute of Ecology and Biological Resources, VAST.

2.3. Extraction and isolation

The dried twigs and leaves of *K. squamulosa* (4 kg) were cut into pieces and extracted with MeOH (10 L × 3 times) at room temperature. The methanol solution was concentrated using a rotatory evaporator to give a residue of the MeOH extract (300 g), which was further suspended in H_2O and successively partitioned with *n*-hexane (H) and EtOAc to afford H (56 g), E (20 g), and aqueous extracts (W). E extract (20 g) was subjected to *silica gel* column chromatography (CC) and eluted with a gradient mixture of *n*-hexane-acetone (100:1 to 0:1, v/v) and CH_2Cl_2-MeOH (20:1 to 0:1, v/v) to yield nine fractions (E1-E9). Fraction E5 (3.5 g) was separated by RP C_{18} CC, with eluent of MeOH-H_2O (1:2, v/v) to

give five subfractions, E5A-E5E., compounds **1** (25 mg) and **4** (15 mg) was purified from subfraction E5C (500 mg) by Sephadex™ LH-20 CC [MeOH-H_2O (1:1, v/v)] and *silica gel* CC [CH_2Cl_2-acetone (1:1, v/v)]. Subfraction E5A (580 mg) was purified by RP C_{18} CC, eluting with MeOH-H_2O (2:1, v/v), to yield **2** (3.8 mg). Fraction E4 (4 g) was further subjected to a fractionation over reversed phase (RP) C_{18}, eluting with MeOH-H_2O (1:2, v/v) to obtain eight subfractions (E4A-E4H). Isolation of subfraction E4E (200 mg) by Sephadex™ LH-20 CC, using mobile phase of MeOH-H_2O (1:1, v/v) to obtain **3** (12 mg) and **5** (4 mg). Fraction E4B (150 mg) was purified by RP C_{18} CC (MeOH-H_2O, 2:1, v/v) and followed by separation over Sephadex™ LH-20, using elution of MeOH-H_2O (1:1, v/v) to afford **6** (9 mg). Fraction E5D (400 mg) was separated by *silica gel* CC, eluting with CH_2Cl_2-acetone (3:1, v/v) to yield **7** (2.8 mg).

Sulfuretin (1): pale-yellow oil. ^{1}H NMR (DMSO-d_6, 600 MHz): δ_H 6.64 (1H, s, H-2), 7.59 (1H, d, J = 8.4 Hz, H-5), 6.70 (1H, br d, J = 8.4 Hz, H-6), 6.75 (1H, br s, H-8), 7.45 (1H, d, J = 1.8 Hz, H-2'), 6.84 (1H, d, J = 8.4 Hz, H-5'), 7.28 (1H, dd, J = 1.8, 7.8 Hz, H-6'). ^{13}C NMR (150 MHz, DMSO-d_6): see Table **1**.

(-)-3,4',7-Trihydroxy-3'-methoxyflavan (2): pale-yellow oil, $[\alpha]_D^{25}$ = - 37.8° (*c* 0.08, MeOH); CD (MeOH) λ_{max} (mdeg): 243 (+ 0.34), 288 (- 1.11) nm. ^{1}H-NMR (600 MHz, CD_3OD+$CDCl_3$): δ_H 4.67 (1H, d, J = 7.8 Hz, H-2), 4.05 (1H, m, H-3), 2.76 (1H, dd, J = 9.0, 15.6 Hz, H_a-4), 2.96 (1H, dd, J = 5.4, 15.6 Hz, H_b-4), 6.88 (1H, d, J = 8.4 Hz, H-5), 6.39 (1H, dd, J = 2.4, 8.4 Hz, H-6), 6.36 (1H, d, J = 2.4 Hz, H-8), 6.93 (1H, d, J = 1.8 Hz, H-2'), 6.84 (1H, d, J = 7.8 Hz, H-5'), 6.86 (1H, dd, J = 1.8, 7.8 Hz, H-6'), 3.85 (3H, s, OCH_3); ^{13}C-NMR (150 MHz, CD_3OD+$CDCl_3$): see Table 1.

7-Hydroxy-3',4'-methylenedioxyflavan (3): pale-yellow oil, $[\alpha]_D^{25}$ = - 34.3° (*c* 0.1, MeOH). ^{1}H NMR (DMSO-d_6, 600MHz): δ_H 4.93 (1H, d, J = 9.6 Hz, H-2), 1.92 (1H, m, H_a-3), 2.04 (1H, m, H_b-3), 2.57 (1H, m, H_a-4), 2.78 (1H, m, H_b-4), 6.84 (1H, d, J = 8.4 Hz, H-5), 6.30 (1H, dd, J = 2.4, 7.8 Hz, H-6), 6.21 (1H, d, J = 2.4 Hz, H-8), 6.95 (1H, br s, H-2'), 6.89 (1H, H-5'), 6.89 (1H, H-6'), 6.00 (2H, d, J = 1.8 Hz, O-CH_2-O); ^{13}C-NMR (150 MHz, DMSO-d_6): see Table 1.

(-)-Liquiritigenin (4): pale-yellow oil, $[\alpha]_D^{25}$ = - 19.6° (*c* 0.07, MeOH). ^{1}H NMR (DMSO-d_6, 600 MHz): δ_H 5.34 (1H, dd, J = 3.0, 13.2 Hz, H-2), 2.61 (1H, dd, J = 3.0, 16.8 Hz, H_a-3), 3.10 (1H, dd, J = 13.2, 16.8 Hz, H_b-3), 7.63 (1H, d, J = 9.0 Hz, H-5), 6.49 (1H, dd, J = 2.4, 8.4 Hz, H-6), 6.32 (1H, d, J = 2.4 Hz, H-8), 7.32 (2H, d, J = 8.4 Hz, H-2', H-6'), 6.78 (2H, d, J = 8.4 Hz, H-3', H-5'); ^{13}C-NMR (150 MHz, DMSO-d_6): see Table 1.

Eriodictyol (5): pale-yellow oil, $[\alpha]_D^{25}$ = - 14.5° (*c* 0.1, MeOH). ^{1}H NMR (DMSO-d_6, 600 MHz): δ_H 5.38 (1H, dd, J = 3.0, 12.0 Hz, H-2), 2.68 (1H, 1H, dd, J = 3.0, 16.8 Hz, H_a-3), 3.18 (1H, 1H, d, J = 12.6, 16.8 Hz, H_b-3), 5.88 (1H, d, J = 2.4 Hz, H-6), 5.89 (1H, d, J = 2.4 Hz, H-8), 6.87 (1H, br s, H-2'), 6.75 (2H, H-5', H-6'); ^{13}C-NMR (150 MHz, DMSO-d_6): see Table 1.

Chysoeriol (6): pale-yellow oil, ^{1}H-NMR (600 MHz, DMSO-d_6): δ_H 6.88 (1H, d, J = 1.8 Hz, H-3), 6.19 (1H, d, J = 1.8 Hz, H-6), 6.50 (1H, d, J = 1.8 Hz, H-8), 7.54 (1H, br s, H-2'), 6.93 (1H, d, J = 7.8 Hz, H-5'), 7.56 (1H, dd, J = 2.4, 7.8 Hz, H-6'), 3.89 (3H, s, 3'-OCH_3); ^{13}C-NMR (150 MHz, DMSO-d_6): see Table 1.

Luteolin (7): pale-yellow oil, ^{1}H-NMR (600 MHz, DMSO-d_6): δ_H 6.66 (1H, s, H-3), 6.18 (1H, d, J = 2.4 Hz, H-6), 6.44 (1H, d, J = 2.4 Hz, H-8), 7.39 (1H, d, J = 1.8 Hz, H-2'), 6.88 (1H, d, J = 8.4 Hz, H-5'), 7.40 (1H, dd, J = 2.4, 8.4 Hz, H-6'); ^{13}C-NMR (150 MHz, DMSO-d_6): see Table 1.

2.4. Antimicrobial assay

Antimicrobial effects of compounds **1-7** toward the Gram-positive bacterial strains *E. faecalis* (ATCC13124), *S. aureus* (ATCC25923), and *B. cereus* (ATCC13245), Gram-negative bacterial strains *E. coli* (ATCC25922), *P. aeruginosa* (ATCC27853), and *S. enterica* (ATCC12228), and a yeast strain *C. albicans* (ATCC1023) were tested using a micro broth dilution method in 96-well microplates. Minimum inhibitory concentration (MIC) values of the compounds were determined by micro broth dilution method in 96-well microplates. MIC was considered as the lowest concentration of an antimicrobial agent that completely inhibited the visible growth of tested microorganisms. The stock solution of the tested compounds was diluted with DMSO to make a series of concentrations in a range from 2 to 512 µM, and the final volume was 100 µL. After that, the microbial strains (each 5 × 10^5 CFU/mL) were added, and the plates were incubated at 37°C for 24 h. The absorbance was measured using a Biotek microplate reader at the wavelength 650 nm. The sample that inhibited the growth of the bacteria at the minimum concentration was assigned as MIC. Streptomycin and cyclohexamide were used as the positive controls at the concentration range from 8 to 512 µg/mL [10,11]. The experiment was

conducted in triplicate for every sample.

3. Results and discussion

A MeOH extract of the twigs and leaves of *K. squamulosa* was suspended in H_2O and successively partitioned with *n*-hexane, and EtOAc. The EtOAc residue was fractionated by repeated column chromatography over *silica gel*, RP-C18, and Sephadex LH-20, to afford eight compounds (**1**–**7**).

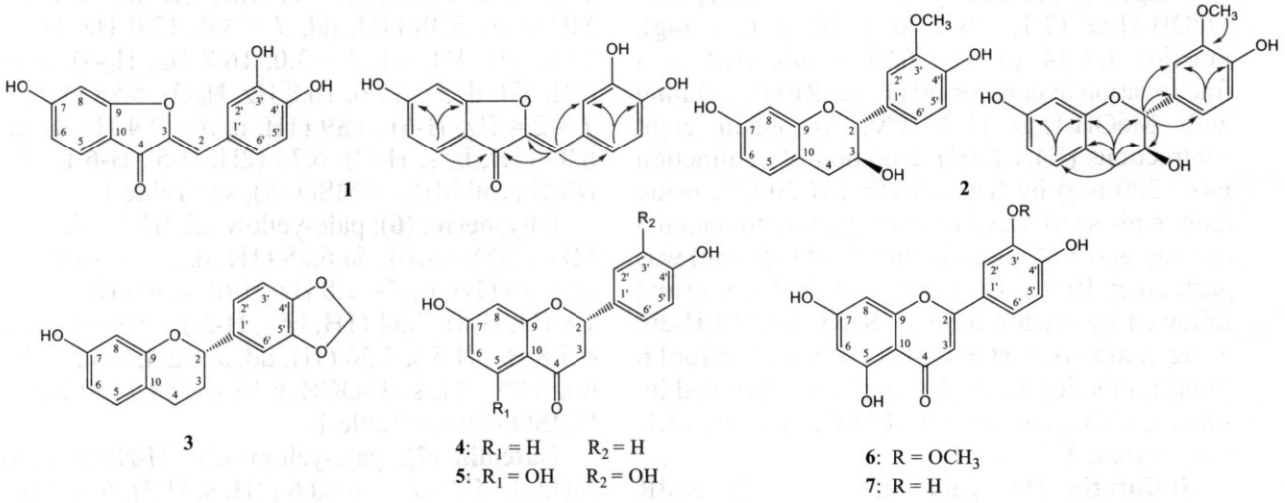

Fig. 1. Structures of compounds **1**–**7** isolated and key HMBC correlations (→) of **1, 2**

Compound **1** was obtained as pale-yellow oil. The ^{1}H-NMR spectrum of **1** exhibited signals for 7 olefinic protons including two aromatic rings ABX at δ_H 7.59 (1H, d, J = 8.4 Hz, H-5), 6.70 (1H, br d, J = 8.4 Hz, H-6), 6.75 (1H, br s, H-8) and δ_H 7.45 (1H, d, J = 1.8 Hz, H-2'), 6.84 (1H, d, J = 8.4 Hz, H-5'), 7.28 (1H, dd, J = 1.8, 7.8 Hz, H-6'), and a singlet at δ_H 6.44 (1H, s, H-2). The ^{13}C NMR spectrum of **1** showed 15 carbon signals, including those of two aromatic rings at δ_C 125.69 (C-5), 112.85 (C-6), 167.42 (C-7), 98.35 (C-8), 166.14 (C-9), 113.19 (C-10), 123.29 (C-1'), 117.93 (C-2'), 145.52 (C-3'), 147.99 (C-4'), 116.01 (C-5'), 124.53 (C-6'), a double bond δ_C 111.9 (C-2)/145.7 (C-3), and a carbonyl group at δ_C 181.2 (C-4). The HMBC spectrum showed a correlation between H-2 (δ_H 6.64) and C-2' (δ_C 117.9), C-6' (δ_C 124.5), C-3 (δ_C 145.7), and C-4 (δ_C 181.2) and verified for the occurrence of an aurone skeleton. By detailed analysis of the key HMBC correlations (Fig.1), the structure of **1** was clearly identified as (2*Z*)-2-(3,4-dihydroxybenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one, with the name sulfuretin. Previously, sulfuretin was isolated from *Bidens parviflora* and *Dipteryx lacunifera* [12, 13]. To the best of our knowledge, this is the first report on compound **1** from the genus *Knema*.

The ^{1}H- and ^{13}C NMR and the optical rotation values of compound **2** were identical with those of (-)-3,4',7-trihydroxy-3'-methoxyflavan, suggesting both compounds have the same structures [14]. However, the large coupling constants [$J_{2,3}$ = 7.8 Hz in **2** and $J_{2,3}$ = 7.5 Hz in (-)-3,4',7-trihydroxy-3'-methoxyflavan] were indicative of the *trans*-arrangement of H-2 and H-3 for both compounds [15]. This was further confirmed by the CD spectroscopy. Accordingly, the CD spectrum of **2** displayed a negative Cotton effect at 288 nm, indicating that **2** has 2*R*,3*S* configurations [16]. Therefore, the structure of **2** was assigned as (-)-3,4',7-trihydroxy-3'-methoxyflavan, with 2*R*,3*S* absolute configurations.

Compound **6** was determined to be a flavone on the basis of signals in the ^{1}H NMR spectrum at δ_H 6.88 (1H, d, J = 1.8 Hz, H-3), 6.19 (1H, d, J = 1.8 Hz, H-6), 6.50 (1H, d, J = 1.8 Hz, H-8), 7.54 (1H, br s, H-2'), 6.93 (1H, d, J = 7.8 Hz, H-5'), 7.56 (1H, dd, J = 2.4, 7.8 Hz, H-6'). The ^{13}C NMR spectra of **6** showed 16 signals, including one conjugated C=O group at δ_C 181.8, one methoxy group at δ_C 56.0 and 14 aromatic carbons. The HMBC correlations from methoxy protons (δ_H 3.89) to C-3'; H-5' to C-1', C-3', C-4'; H-6' to C-2, C-2', C-4' clearly confirmed the structure of **6** as shown in Fig.1. Thus, **6** was identified as chrysoeriol [17].

Similarly, the other compounds were also identified on the basis of their NMR and specific optical rotation values and by comparison with literature data: 7-hydroxy-3',4'-methylenedioxyflavan (**3**) [18], (-)-liquiritigenin (**4**) [19], eriodictyol (**5**), and luteolin (**7**) [17].

Table 1. The ^{13}C NMR data (150 MHz) of compounds **1-7**

C	1[+]	2[+++]	3[+]	4[+]	5[+]	6[+]	7[+]
2	111.9	72.4	76.8	79.0	78.4	163.7	163.9
3	145.7	68.1	29.5	43.2	42.1	103.2	102.9
4	181.2	33.0	23.7	190.1	196.3	181.8	181.7
5	125.7	130.6	129.9	128.4	163.4	161.4	161.5
6	112.9	109.1	108.1	110.5	95.7	98.8	98.8
7	167.4	156.8	156.5	164.6	162.9	164.2	164.1
8	98.6	103.2	102.8	102.6	94.9	94.1	93.9
9	166.1	155.2	155.3	163.2	166.6	157.3	157.3
10	113.2	111.9	112.2	113.5	101.8	103.7	103.7
1'	123.3	130.8	135.7	129.3	129.4	121.5	121.5
2'	117.9	110.8	119.6	128.3	114.4	110.2	113.4
3'	145.5	147.9	108.0	115.1	145.2	148.0	145.8
4'	148.0	146.6	147.3	157.6	145.7	150.7	149.7
5'	116.0	115.3	146.7	115.1	115.3	115.8	116.0
6'	124.5	120.7	106.7	128.3	117.9	120.4	119.0
OCH_3		56.1				56.0	
$O\text{-}CH_2\text{-}O$			101.0				

[+] Measured in DMSO-d_6, [++] in CD_3OD, [+++] in CD_3OD+$CDCl_3$.

Table 2. Antimicrobial effect of compounds **1-7**

Compounds	MIC values (µM)						
	Enterococcus faecalis ATCC299212	*Staphylococcus aureus* ATCC25923	*Bacillus cereus* ATCC13245	*Escherichia coli* ATCC25922	*Pseudomonas aeruginosa* ATCC27853	*Salmonella enterica* ATCC13076	*Candida albicans* ATCC10231
1	150	150	150	-	-	-	150
2	150	-	-	-	-	-	-
3	300	150	-	-	-	-	-
4	150	-	150	-	-	-	-
5	150	-	-	-	-	-	-
6	150	-	-	-	-	-	-
7	150	-	-	-	-	-	-
Streptomycin*	440	440	220	55	440	220	-
Cyclohexamide*	-	-					114

(-): inactive; (*) positive control.

Antimicrobial assay indicated that all the compounds inhibited the growth of *E. faecalis* ATCC299212 with MIC values ranging from 150 to 300 µM (Table 2). In addition, compound **1** suppressed the growth of *S. aureus* ATCC25923, *B. cereus* ATCC14579, and the yeast *C. albicans* ATCC10231, with MIC values of 150 µM, compounds **3** and **4** showed antimicrobial effects against *S. aureus* ATCC25923 and *B. cereus* ATCC13245, with MIC values of 150 µM, whereas all the compounds were inactive against all the tested Gram-negative bacteria. The experimental results were consistent with the fact that the Gram-positive bacteria (particularly *E. faecalis* ATCC299212) are more susceptible to the antibiotics due to their lack of the outer membrane than the Gram-negative ones [20].

4. Conclusion

Chemical study of the methanolic extract of *K. squamulosa* twigs and leaves obtained eight compounds, including sulfuretin (**1**), (-)-3,4',7-trihydroxy-3'-methoxyflavan (**2**), 7-hydroxy-3',4'-methylenedioxyflavan (**3**), (-)-liquiritigenin (**4**), eriodictyol (**5**), chysoeriol (**6**), and luteolin (**7**). Up to now, this is the first instance of compounds **1**, **2**, and **4** found at the *Knema* genus. To the best of our knowledge, this is the first report on the chemical constituents from *K. squamulosa*, hence, these metabolites could be valuable chemotaxonomic markers for the identification of the species in the Myristicaceae family. Additionally, of the compounds, **1** showed antimicrobial effect against all three Gram-positive bacteria and the yeast, each of **3** and **4** inhibited the growth of two Gram-positive bacteria, while other compounds only suppressed the growth of *E. faecalis*. Our results contribute to understanding the secondary metabolites produced by *K. squamulosa* and provide a scientific rationale for further studies of the antimicrobial activity for the plant.

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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.