A New 2,3-Dioxygenated Flavanone and Other Constituents from *Dysosma difformis*

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**Abstract:** A novel 2,3-dioxygenated flavanone, dysosmaflavanone (2), along with five known phenolic compounds including podophyllotoxin (1), podoverin A (3), kaempferol (4), 8,2′-diprenyl quercetin 3-methyl ether (5), and ethyl β-D-glucoside (6) were isolated from the roots of the plant *Dysosma difformis*. Their structures were elucidated via spectroscopic analysis. Besides podophyllotoxin and kaempferol, the rest of the compounds were isolated from the genus *Dysosma* for the first time. Dysosmaflavanone, which possesses a rare 2,3-dioxygenated skeleton, could be regarded as an important chemotaxonomic marker. The antioxidant and antidiabetic activities of the isolated compounds were evaluated.

**Keywords:** *Dysosma difformis*; Berberidaceae; 2,3-dioxygenated flavanone; dysosmaflavanone. © 2021 ACG Publications. All rights reserved.

1. Introduction

*Dysosma difformis* (Hemsl. & E.H.Wilson) T.H.Wang (syn: *Podophyllum tonkinense* Gagnep) (Berberidaceae) is widely used as a traditional medicine to treat sore throats, pimples, and snakebites [1]. Aglycone, aryltetralin lignan glycosides, and flavonols [2–5], which exhibit antiproliferative [6], anticancer [7], and angiogenesis-inhibiting [8] activities, are produced by species of the *Dysosma* genus. Podophyllotoxin (1), the major aryltetralin lignan in *Dysosma* plants, exhibits anticancer properties [9]. However, few investigations into the phytochemical constituents of *D. difformis* have been conducted [10, 11]. In the present study, we describe the isolation and structure of a new 2,3-dioxygenated flavanone (2) and five other known compounds isolated from the roots of *D. difformis* (Figure 1).

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2. Materials and Methods

2.1. Plant Material

The underground parts of *Dysosma difformis* were collected from Ha Giang province, Vietnam, in December 2018. The sample was identified by one of the authors (Bui Van Thanh) and a voucher specimen (No. Berb_HG_10) was deposited at the herbarium of the Institute of Ecology and Biological Resources.

2.2. General Procedures

NMR experiments were performed on a Bruker AM500 FT-NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Optical rotations were read on a JASCO P-2000 digital polarimeter. High-resolution mass spectra (ESI positive mode) were obtained with a Thermo LTQ Orbitrap XL mass spectrometer. Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F$_{254}$ plates (Merck, Germany), and spots were detected under UV illumination 254 nm and spraying with H$_2$SO$_4$ 10% reagents followed by heating. Column chromatography (CC) was carried out using D101 resin (0.3-1.5 mm, Extrepure, China), silica gel 60 (70-230 mesh, Merck, Germany), or YMC RP-C18 resin (150 μm, YMC, Japan). Preparative HPLC was conducted on a Thermo Dionex Ultimate 3000 system, using a YMC-Pack ODS-A (5 μm, 250 x 20 mm i.d., YMC Co., Ltd., Kyoto, Japan) column, with a 5 mL/min flow rate.

2.3. Extraction and Isolation

The air-dried powdered materials (1.3 kg) were extracted with ethanol (EtOH) (2 L × 4 times) in an ultrasonic bath for 30 min. The combined extracts were concentrated to obtain an ethanol crude residue (160.5 g), which was then loaded on a column (300 x 100 mm i.d.) filled with 1 kg of D101 resin. After the sample was completely adsorbed, the column was eluted by 10 L of deionized water,
New 2,3-dioxygenated flavanone from *Dysosma difformis*

following by increasing concentrations of MeOH (25%, 50%, and 100%) in water, to obtain four fractions, F1-F4. Fraction F3 was subjected to a silica gel CC with gradient mixtures of n-hexane–acetone (10/1-1/1, v/v) to afford eleven subfractions (F3.1 – F3.11). Fraction F3.7 was separated using silica gel eluted with CH$_2$Cl$_2$–MeOH (70/1, v/v) to yield podophyllotoxin (1) (416.6 mg) and ten subfractions (F3.7.2-F3.7.11). Fraction F3.7.6 was purified by preparative HPLC (60 min, 40-75% MeOH in H$_2$O) to afford the new flavanonol, dysosmaflavanone (2) (9.1 mg), and podoverin A (3) (40.1 mg). Kaempferol (4) (53.9 mg) was purified by recrystallizing the fraction F3.7.11 in MeOH–H$_2$O (1/1, v/v). Fraction F3.6 was isolated using a silica gel column eluted with CH$_2$Cl$_2$–MeOH (60/1, v/v), following by a YMC RP-C18 column eluted with MeOH–water (3:1, v/v) to yield 8,2’-diprenyl quercetin 3-methyl ether (5) (7.5 mg).

Fraction F2 was chromatographed on a silica gel column and eluted with CH$_2$Cl$_2$–MeOH–H$_2$O (5/1/0.1, v/v/v) to yield ethyl β-D-glucoside (6) (75.3 mg). The purity of all isolated compounds was > 97% via HPLC (data not shown).

*Dysosmaflavanone* (2): Pale yellow powder; [α]$_D^{25}$ +0.15 (c 0.2, MeOH); HRMS (ESI positive) m/z 389.1218 ([M+H]$^+$, calcd for C$_{20}$H$_{21}$O$_8$, 389.1236), 411.1070 ([M+H]$^+$, calcd for C$_{20}$H$_{20}$O$_8$Na, 411.1056), 799.259 (2M+Na)$^+$, 373.0957 ([M-CH$_3$]$^+$), 343.0864 ([M-OC$_2$H$_5$]$^+$). NMR data of the compound in CD$_3$OD and DMSO-d$_6$ were shown in Table 1.

2.4. DPPH Radical Scavenging Assay

2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity was conducted by modified a previous method [12]. Briefly, 10 μL of each sample was mixed with 190 μL of DPPH (Sigma-Aldrich) in methanol before incubated at 37°C for 20 minutes. The absorbance was measured at 517 nm. Ascorbic acid was used as a positive control.

2.5. Superoxide Radical Scavenging Assay

Superoxide radical scavenging activity was measured by a reported method with some modification [13]. In brief, 100 μL of the sample dissolved in DMSO was mixed with 300 μL of the phosphate buffer 50 mM pH 7.8, 200 μL xanthine 0.5 mM, 100 μL nitroblue tetrazolium 0.2 mM, and 100 μL of xanthine oxidase. The mixture was incubated at 37°C for 60 minutes then measured at the wavelength of 550 nm. (+)-catechin was used as a positive control.

2.6. Hydroxyl Radical Scavenging Assay

Hydroxyl radical inhibition was evaluated by a modified method of the previously reported assay [13]. The mixture containing 50 μL of the test sample, 100 μL of the phosphate buffer 50 mM pH 7.8, 100 μL of deoxyribose 2.8 mM, and 100 μL of Fe(NH$_4$)$_2$(SO$_4$)$_2$ 500 μM was incubated for 1 h at 37 °C. After adding 250 μL of trichloroacetic acid (10%, w/v) and 250 μL of thiobarbituric acid (1%, w/v), the reaction mixture was boiled for 15 min in a water bath. The color development was measured at 532 nm. (+)-catechin was used as a positive control.

2.7. α-Glucosidase Inhibition Assay

The α-glucosidase enzyme inhibition activity was assessed by modifying a previous method [14]. 50 μL of the sample solution in methanol was mixed with 100 μL of α-glucosidase (G0660-750UN, Sigma-Aldrich) 0.5 U/mL and 100 μL of phosphate buffer 100 mM (pH 6.8-7.0). After 10 min of pre-incubation at room temperature, 50 μL of 5 mM p-nitrophenyl-α-D-glucopyranoside solution was added, and the solution was incubated at 37°C for 30 min. The absorbance of released 4-nitrophenol was measured at 405 nm by using a microplate reader. Acarbose was used as a positive control.

2.8. α-Amylase Inhibition Assay
The α-amylase enzyme inhibitory activity was evaluated by the previously reported method [14] with some modifications. The substrate was prepared by boiling 80 mg of potato starch in 4 mL phosphate buffer (pH 7.0) for 5 min, then it was left at room temperature to cool down. Next, 100 μL of the sample solution was mixed with 50 μL of the substrate and 30 mL of 100 mM phosphate buffer (pH 7.0). After 5 min of pre-incubation, 50 μg/mL α-amylase (A8220, Sigma-Aldrich) solution was added, and the solution was incubated at 37°C for 15 min. The reaction was stopped by adding 50 μL of glacial acetic acid, then 50 mL iodine solution was added. The absorbances were measured at 650 nm by using a microplate reader. Acarbose was used as a positive control.

3. Results and Discussion

3.1. Structure Elucidation

Compound 2 was obtained as a pale-yellow powder, which generated [M+H]^+ and [M+Na]^+ ions with mass-to-charge ratio (m/z) values of 389.1218 and 411.0864 [M-OC2H5] showed the presence of an ethoxy group when analysed by high-resolution electrospray ionization mass spectrometry; this suggested that the compound had a molecular formula of C20H20O8. Fragment ions with m/z 373.0957 [M - CH3]^+ and 343.0864 [M - OC2H5]^+ revealed the presence of an ethoxy group in the compound 2 structure. H NMR analysis of compound 2 also indicated an ethoxy group [3.37 (1H, dq, overlap, H-1a’’), 3.52 (1H, dq, J = 7.5, 2.5 Hz, H-1b’’), 1.04 (3H, t, J = 7.5 Hz, H-2’’)] and protons in an acetonyl system [2.25 (1H, d, J = 15.5 Hz, H-1a’’), 3.08 (1H, d, J = 15.5 Hz, H-1b’’), 2.28 (3H, s, H-3’’)]. In addition, two meta-coupled doublets [5.99 (1H, d, J = 2.5 Hz, H-6), 6.01 (1H, d, J = 2.5 Hz, H-8)] and an A2B2-system [7.43 (2H, d, J = 8.5 Hz, H-2’, 6’), 6.84 (2H, d, J = 8.5 Hz, H-3’, 5’)] were detected, indicative of a flavonoid skeleton with a symmetrical B-ring.

Table 1. 1H (500 MHz) and 13C (125 MHz) NMR data for compound 2

| Position | δC (CD3OD) | δH (CD3OD) | δC (DMSO-d6) | δH (DMSO-d6) |
|----------|------------|------------|--------------|--------------|
| 2        | 108.9      | 107.5      |              |              |
| 3        | 79.8       | 77.1       |              |              |
| 4        | 196.5      | 194.6      |              |              |
| 4a       | 100.8      | 99.2       |              |              |
| 5        | 165.5      | 163.4      |              |              |
| 6        | 97.5       | 5.99 (1H, d, J = 2.5 Hz) | 96.5 | 5.97 (1H, brs) |
| 7        | 168.3      |            | 166.8        |              |
| 8        | 96.7       | 6.01 (1H, d, J = 2.5 Hz) | 95.6 | 5.97 (1H, brs) |
| 8a       | 160.1      |            | 158.4        |              |
| 1’       | 126.6      |            | 124.4        |              |
| 2’; 6’   | 131.0      | 7.43 (2H, d, J = 8.5 Hz) | 129.7 | 7.32 (2H, d, J = 8.5 Hz) |
| 3’, 5’   | 115.5      | 6.84 (2H, d, J = 8.5 Hz) | 114.5 | 6.82 (2H, d, J = 8.5 Hz) |
| 4’       | 159.5      |            | 158.1        |              |
| 1”       | 60.3       | 3.37 (1H, dq, overlap) | 58.9 | 3.42 (1H, dq, overlap) |
| 2”       | 15.1       | 1.04 (3H, t, J = 7.5 Hz) | 14.7 | 0.94 (3H, t, J = 7.5 Hz) |
| 1””      | 41.7       | 2.25 (1H, d, J = 15.5 Hz) | 42.5 | 2.28 (1H, d, J = 15.5 Hz) |
| 2””      | 213.9      |            | 209.0        |              |
| 3””      | 31.8       | 2.28 (3H, s) | 31.2 | 2.10 (3H, s) |
| 3-OH     |            |            | 6.33 (1H, brs) |              |
| 5-OH     |            |            | 11.28 (1H, brs) |              |
| 7-OH     |            |            | 10.90 (1H, brs) |              |
| 4’-OH    |            |            | 9.66 (1H, s)       |              |

Twenty carbons were detected via 13C NMR, including ten quaternary carbons, six methines, two methylenes, and two methyl groups, which were confirmed via heteronuclear single quantum
coherence. Carbon chemical shifts indicated two carbonyl groups (δc 196.5 and 213.9), four oxygenated aromatic carbons (δc 165.5, 168.3, 160.1, and 159.5), a doubly oxygenated sp3 (δc 108.9), an oxygenated aliphatic carbon (δc 79.8), and two other aromatic carbons (δc 126.6 and 100.8). Erigeroflavanone [15] is a 2,3-dioxygenated flavanone containing an ethoxy group, an acetoxy group, and four hydroxyl groups. Heteronuclear multiple bond correlations (HMBCs) (Figure 2) between H2-1" (δh 3.37, 3.52) and C-2 (δc 108.9) revealed that the ethoxy group was located at position C-2. Furthermore, HMBCs between H2-1" (δh 3.08, 2.25) and C-2 (δc 108.9), C-3 (δc 79.8), and C-4 (δc 196.5) revealed an acetonyl group located at C-3. The molecular profile of compound 2 was similar to that of the flavanone cepaflava B [16]; however, cepaflava B contains a methoxy group at C-3 and an ABX system (Table S1).

The near-zero optical rotation and lack of significant Cotton effect on the compound 2 circular dichroism spectrum (data not shown) suggested that the mixture was racemic. To observe the -OH groups of compound 2 in more detail, one-dimensional and two-dimensional NMR experiments were conducted using deuterated dimethyl sulfoxide. Nuclear Overhauser effect spectroscopy revealed correlations between the 3-OH proton and H-1", and between H-1" and H-3', while there was no correlation between H-1" and H-1" (Figures 2 and S12); this suggested an erythro-orientation between the ethoxy group at C-2 and the hydroxyl group at C-3 of compound 2. Thus, we determined compound 2 to be (2RS,3SR)-2-ethoxy-3,5,7-trihydroxy-2-(4-hydroxyphenyl)-3-(2-oxopropyl)-chroman-4-one and named the compound “dysosmaflavanone”.

![Figure 2. Key HMBC (——) and NOESY (-----) correlations of the compound 2](image)

Next, we performed high-performance liquid chromatography (HPLC) to further examine compound 2. Extractions were performed on the roots of D. difformis with methanol and acetone, then analysed with an HPLC-diode array detector system. Compound 2 was not detected in the methanol or acetone extracts (data not shown), suggesting that the compound was an artefact of the ethanol extraction process. Recently, similar 2,3-dioxygenated flavanones were discovered to be artificial products generated during flavonoid extraction from plant materials [16]. Furthermore, flavonoids that are oxygenated at both the C-2 and C-3 positions are rarely found in nature [15, 17]; thus, the origin of compound 2 must be investigated further.

The other five isolated phenolic compounds, podophyllotoxin (1) [18], podoverine A (3) [19], kaempferol (4) [20], 8,2’-diprenyl quercetin 3-methyl ether (5) [21], and ethyl β-D-glucoside (6) [22], were identified by comparing our NMR data to previous reports. Podophyllotoxin (1) is an effective anticancer agent [23] and 8,2’-diprenyl quercetin 3-methyl ether (5) is significantly more cytotoxic against human mammary adenocarcinoma and breast cancer cell lines compared to taxol [21].

3.2. Biological Activities

In this study, the isolated compounds were evaluated for their antioxidant capacity via scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl, and superoxide radicals. Their antidiabetic activity was also tested on digestive enzymes α-glucosidase and α-amylase. As shown in Table 2, the five phenolic compounds exhibited higher DPPH scavenging activity than ascorbic acid, while showing weaker hydroxyl radical and superoxide radical inhibition compared to catechin. The inhibitory activities of all isolated compounds against α-glucosidase and α-amylase were evaluated in comparison with acarbose, an antidiabetic agent. Dysosmaflavanone inhibited α-glucosidase and α-
amylase activities at lower doses than acarbose. Among the six compounds, kaempferol showed the highest antioxidant and while 8,2'-diprenyl quercetin 3-methyl ether exhibited strongest inhibition against digestive enzymes, while ethyl β-D-glucoside did not exhibit any antioxidant or antidiabetic activity. The new dysosmaflavanone showed similar effects with kaempferol in inhibiting α-glucosidase and α-amylase.

Table 2. Inhibitory effects* of the isolated compounds against free radicals and digestive enzymes

| Compounds                        | DPPH    | OH•     | O₂•     | α-glucosidase | α-amylase |
|----------------------------------|---------|---------|---------|---------------|-----------|
| Podophyllotoxin (1)              | 28.6 ± 1.1 | 61.2 ± 3.0 | 77.2 ± 6.2 | 1500 ± 131   | 1703 ± 99  |
| Dysosmaflavanone (2)             | 35.2 ± 2.9 | 20.3 ± 1.7 | 69.7 ± 5.0 | 1382 ± 120   | 1330 ± 111 |
| Podoverine A (3)                 | 42.3 ± 2.4 | 22.8 ± 1.8 | 65.4 ± 3.7 | 1962 ± 169   | 1297 ± 109 |
| Kaempferol (4)                   | 17.7 ± 0.9 | 12.9 ± 0.9 | 42.3 ± 1.1 | 1360 ± 105   | 1246 ± 117 |
| 8,2'-Diprenyl Quercetin 3-methyl ether (5) | 44.4 ± 3.0 | 34.6 ± 2.8 | 56.5 ± 4.4 | 1057 ± 82    | 857.8 ± 78.3 |
| Ethyl β-D-glucoside (6)          | >100     | >100     | >100     | >3000         | >3000      |
| Ascorbic acid                    | 55.3 ± 1.8 | _        | _        | _             | _          |
| (+)-Catechin                     | _        | 18.9 ± 1.05 | 32.1 ± 2.5 | _             | _          |
| Acarbose                         | _        | _        | _        | 1020 ± 85    | 623.9 ± 60.2 |

*IC₅₀ values in µM are mean ± SD from triplicate experiments.

3.3. Chemotaxonomy

In the present investigation, we isolated and identified six metabolites from the roots of *D. difformis* (Berberidaceae), including one aryltetralin lignan, three flavonols, a novel 2,3-dioxygenated flavanone, and an alkyl glucoside. Our findings highlight the need for further chemotaxonomic studies of the *Dysosma* genus and the Berberidaceae family. Podophyllotoxin (1) has previously been isolated from the *Dysosma* [3], *Sinopodophyllum* [24], *Podophyllum* [25], and *Diphylleia* [18] genera of the Berberidaceae family. However, this compound is not present in other well-known genera in the same family, such as *Epimedium, Vancouveria, Mahonia*, and *Berberis*. Thus, podophyllotoxin might be a valuable marker for distinguishing between plants within the Berberidaceae family. Moreover, we isolated podoverin A (3), 8,2'-diprenyl quercetin 3-methyl ether (5), and ethyl β-D-glucoside (6) from a *Dysosma* species for the first time. The discovery of these compounds has extended our phytochemical knowledge of the genus *Dysosma*. While podoverin A (3) is present *Sinopodophyllum* [26] and *Podophyllum* [19] species, 8,2'-diprenyl quercetin 3-methyl ether (5) has only been found in *Sinopodophyllum* [21]; this suggests a close relationship between the *Dysosma* and *Sinopodophyllum* genera. A previous phylogenetic study of Berberidaceae found that the *Dysosma* genus was more closely related to *Sinopodophyllum* than to *Podophyllum*, despite their similar morphology [27]. Therefore, compound 5 could be an important chemotaxonomic marker, enabling the identification of these genera.

Although compound 2 may be an artefact of ethanol extraction, the isolation of dysosmaflavanone (2) may instead have revealed the presence of 2,3-dioxygenated flavanone backbone in *D. difformis*. A variety of flavonoids have been isolated from several Berberidaceae genera [24, 28–33], to our knowledge, this is the report of isolation of a 2,3-dioxygenated flavanone from the family.

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New 2,3-dioxygenated flavanone from *Dysosma difformis*

**Supporting Information**

Supporting information accompanies this paper on [http://www.acgpubs.org/journal/records-of-natural-products](http://www.acgpubs.org/journal/records-of-natural-products)

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