

**DIBENZOCYCLOOCTADIENE LIGNANS ISOLATED FROM THE ROOTS OF *SCHISANDRA CAULIFLORA* AND THEIR NITRIC OXIDE INHIBITION ACTIVITY ON LPS STIMULATED RAW 264.7 CELLS**

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**Abstract**

**Objectives:** To isolate and determine the chemical structure of some compounds from the roots of *Schisandra Cauliflora* and their inhibitory activity on nitric oxide production. **Methods:** The roots of *Schisandra cauliflora*, which were collected in Vinh Phuc in April 2022, were processed before being extracted and isolated to obtain compounds. Compounds structures were elucidated based on extensive spectroscopic analyses, including 1D- and 2D-nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (HR-ESI-MS), and CD spectra. The obtained compounds were evaluated for inhibitory activity on nitric oxide production on LPS stimulated RAW 264.7 cells. **Results and conclusion:** From the methanol extract of the roots of *Schisandra cauliflora*, three dibenzocyclooctadiene lignans were isolated, including *ananonin J*, *ananolignan F*, and *ananolignan C*. Their structures were elucidated. All the compounds inhibited nitric oxide productions on LPS stimulated RAW 264.7 cells with IC<sub>50</sub> values of 45.24 ± 1.46, 41.32 ± 1.45, and 48.71 ± 1.34 μM, respectively, compared to that of the positive control of dexamethasone (IC<sub>50</sub> 14.20 ± 0.54 μM). This is the first time these lignan compounds have been isolated from the roots of *Schisandra cauliflora*.

**Keywords:** *Schisandra cauliflora*; Nitric oxide inhibition activity.

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## INTRODUCTION

Plants of the genus *Schisandra* are often used in folk remedies where they are endemic. Different parts of the plant, such as roots, leaves, stems, and fruits, have been shown to have different effects and uses but are mainly used for liver protection, anti-inflammation, and strengthening the circulatory and digestive systems, etc. [1, 2].

Many studies of the genus *Schisandra* have published the isolation of many lignans and triterpenoids containing unique skeletons, such as the dibenzocyclooctadiene lignan and the schinortriterpenoid skeletons [3, 4, 5]. Due to its structural diversity and wide therapeutic application in traditional medicine, the genus *Schisandra* has received national and international research attention [5, 6].

In 2019, Vietnamese botanists announced that *Schisandra cauliflora* was a new species of the genus *Schisandra*, which was endemic to some northern provinces of Vietnam and rarely found outside those areas [7]. Therefore, the study of this new object will have new results on: *The chemical composition and biological activity leading to new research results, which is the basis for further studies.*

## MATERIALS AND METHODS

### 1. Materials

The roots of *Schisandra cauliflora* were collected in Vinh Phuc in April 2022. Taxonomical authentication was done by a taxonomist, Dr. Bui Van Thanh, Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology (VAST). The voucher specimen was kept at the Institute of Ecology and Biological Resources, VAST, and Vietnam Military Medical University.

#### \* Chemicals and equipment:

Lipopolysaccharides (LPS) from *Escherichia coli* of Sigma Chemical Co. (USA); Dulbecco's Modified Eagle's Medium (DMEM); fetal bovine serum (FBS) of Life Technologies, Inc. (USA); Sodium nitrite, sulfanilamide, N-1-naphthylethylene-diamine dihydrochloride, and dimethyl sulphoxide (DMSO) of Sigma Chemical Co. (USA); chemicals and solvents for chromatography of Sigma, GIBCO, Invitrogen, and Promega, etc. The cell line: RAW 264.7 was produced by Dr. Domenico Delfino, University of Perugia (Italy), and Prof. Dr. Chi-Huang, National Yang-Ming University (Taiwan).

Thin layer chromatography (TLC) performed on Aluminum TLC plate coated normal phase (DC-Alufolien 60 F254, Merck); reversed phase C-18 (150 $\mu$ m, Fujisilica Chemical Ltd). The spots were detected by spraying with an aqueous solution of H<sub>2</sub>SO<sub>4</sub> 5%, followed by heating with a heat gun.

Column chromatography is conducted with the adsorbent normal phase and reversed phase. The particle size of the normal phase silica gel is 0.040 - 0.063mm (240 - 430 mesh, Merck), and reversed phase of YMC (30 - 50 $\mu$ m, Fujisilica Chemical Ltd).

Preparative high-performance liquid chromatography (HPLC) was run on an Agilent 1100 system, including a binary pump, autosampler, DAD detector, and semi-preparative HPLC column YMC sphere ODS H80 (4 $\mu$ m, 20  $\times$  250mm). The flow rate of the isocratic mobile phase was 3 mL/min. The compound was monitored at wavelengths 205, 230, 254, and 280nm. Ambient pressure chromatographic column (open column) was performed using silica gel, reversed-phase C-18, and diaion HP-20 resins as stationary phase.

Nuclear magnetic resonance (NMR): Measured on the Bruker AM500 of the Institute of Chemistry, VAST.

The high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) was acquired on an Agilent 6530 Accurate Mass Q-TOF LC/MS of the Institute of Marine Biochemistry, VAST.

## **2. Methods**

### *\* Extraction and isolation:*

The roots of *Schisandra cauliflora* were dried and pulverized to obtain 1.2kg dried powder, which was sonicated with methanol three times (10L and 2h each time) after removal of solvent to give methanolic residues.

The obtained residues (87g) were suspended with 1.0L of distilled water and then partitioned with dichloromethane. The dichloromethane extract obtained was removed from the solvent by distillation under reduced pressure to obtain a dichloromethane residue (21.2g) and an aqueous layer, respectively.

The dichloromethane fraction impregnated with silica gel and column chromatography with *n*-hexane/acetone gradient solvent system (20/1, 10/1, 5/1, 1/1) obtained four fractions denoted SL1- SL4. The SL4 fraction (2.3g) was isolated by reverse phase chromatography

column R-18 with the solvent system MeOH/H<sub>2</sub>O (1/1) to obtain three fractions: SL4A, SL4B, and SL4C. The SL4A fraction was further isolated on a normal phase silica gel column with the solvent system *n*-hexane/EtOAc (10/1.2) to obtain compound 1 (5.6mg). The SL4B fraction was also further isolated by the normal phase chromatography column with solvent system *n*-hexane/EtOAc (10/1.3) to obtain compound 2 (6.8mg). The SL4C fraction was also further isolated by the normal phase chromatography column with *n*-hexane/EtOAc (10/1.25) solvent system, yielding compound 3 (7.2mg). The structures of the compounds were determined based on the methods of nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HR-ESI-MS).

*\* Method to determine the ability to inhibit NO production of macrophage RAW 264.7 cells:*

RAW 264.7 cells were cultured in DMEM medium with 2mM L-glutamine, 10mM HEPES, 1.0mM sodium pyruvate, and 10% fetal bovine serum (GIBCO) supplement. Cells were cultured after 3 - 5 days with the ratio (1:3) and cultured in a CO<sub>2</sub> incubator at 37°C, 5% CO<sub>2</sub>.

RAW 274.7 cells were placed in a 96-well plate at a concentration of 2 x 10<sup>5</sup> cells/well and incubated in an incubator at 37°C and 5% CO<sub>2</sub> for 24h. Next, the culture medium was removed and replaced with FBS-free DMEM for 3h. Cells were then incubated at different concentrations for 2h before being stimulated to produce NO factor by LPS (10 µg/mL) for 24h.

Negative controls were wells with no sample. The positive control was Dexamethasone (Sigma) at concentrations of 100, 20, 4, and 0.8 µg/mL.

Nitrite (NO<sub>2</sub><sup>-</sup>), which was considered as an indicator for NO generation, was determined using the Griess Reagent System (Promega Cooperation, WI, USA). The nitrite content was measured with a microplate reader at 540nm. The nitrite content of the sample was determined using a NaNO<sub>2</sub> standard curve and compared with a negative control (LPS), determined by the formula:

$$\% \text{ NO inhibition} = 100\% - \frac{C_{\text{NO sample}} \times 100}{C_{\text{NO LPS}}}$$

The test was repeated 3 times. The IC<sub>50</sub> value was determined using TableCurve 2Dv4 computer software.

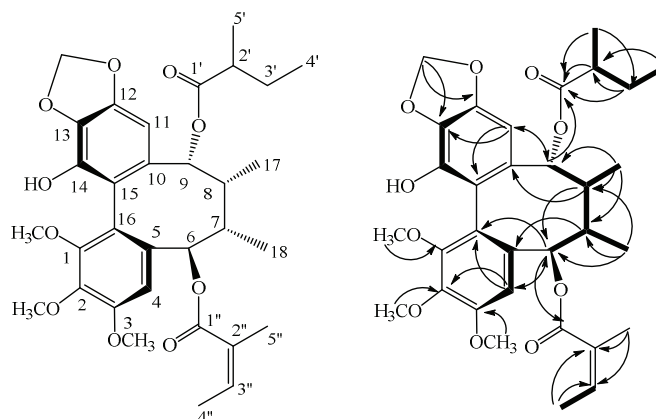
RESULTS AND DISCUSSION

1. Structural identification of isolated compounds

Table 1. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectral data for ananonin J (1).

No.	$\delta_C^{[8]}$	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (J, Hz)	No.	$\delta_C^{[8]}$	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (J, Hz)
1	151.0	150.8	-	17	15.4	16.2	1.02 (d, 7.5)
2	141.9	141.7	-	18	15.4	16.2	0.97 (d, 7.0)
3	152.9	152.7	-	1-OMe	61.1	60.9	3.59 (s)
4	111.0	111.9	6.82 (s)	2-OMe	61.2	60.8	3.90 (s)
5	133.7	133.5	-	3-OMe	56.3	56.1	3.92 (s)
6	81.1	80.8	5.75 (d, 8.5)	OCH <sub>2</sub> O	102.0	101.5	6.00 (d, 1.5) 5.98 (d, 1.5)
7	38.7	38.4	2.10 (m)	1'	176.2	175.9	-
8	39.1	40.3	2.25 (m)	2'	40.5	40.3	1.74 (m)
9	80.6	80.0	5.80 (d, 4.0)	3'	26.8	26.6	1.23 (m); 1.39 (m)
10	133.9	132.8	-	4'	11.4	11.2	0.75 (t, 7.5)
11	101.7	101.7	6.40 (s)	5'	15.3	15.1	0.86 (d, 7.5)
12	148.7	148.4	-	1''	167.1	166.9	-
13	134.7	134.6	-	2''	127.7	127.6	-
14	138.0	137.8	-	3''	139.3	138.8	5.96 (m)
15	118.0	117.8	-	4''	16.0	15.7	1.84 (dd, 3.0, 7.5)
16	120.5	120.0	-	5''	20.4	20.1	1.57 (s)

<sup>a</sup>)CDCl<sub>3</sub>, <sup>b</sup>)125 MHz, <sup>c</sup>)500 MHz. \*The NMR data of ananonin J [8].



**Figure 1.** Structures and key HMBC and COSY correlations of compound 1.

Compound 1 was obtained as white powder,  $n_D^{20} = +72.0$  (c 0.1, MeOH); ECD (0.3 mg/mL in MeOH)  $\theta(\lambda)$ : +3.56(216), -2.34(251) mdeg. Its molecular formula as C<sub>32</sub>H<sub>40</sub>O<sub>10</sub> was determined by the HR-ESI-MS ion peak at m/z 541.2057 [M+Na]<sup>+</sup> (theoretical calculation for [C<sub>32</sub>H<sub>40</sub>O<sub>10</sub>Na]<sup>+</sup>: 541.2049).

The 1D and 2D NMR spectra of compound 1 exhibited the presence of two CH groups connected to the oxygen atom [ $\delta_C/\delta_H$ : 80.8 (C-6)/5.75 (d,  $J = 8.5$  Hz, H-6) and 80.0 (C-9)/5.80 (d,  $J = 4.0$  Hz, H-9) and two CH groups other at [ $\delta_C/\delta_H$ : 38.4 (C-7)/2.10 (m, H-7) and 40.3 (C-8)/2.25 (m, H-8)]; with two methyl groups appearing as doublets at  $\delta_C/\delta_H$  16.2/0.97 (d,  $J = 7.0$  Hz) and 16.2/1.02 (d,  $J = 7.5$  Hz); three methoxy groups ( $\delta_C/\delta_H$  56.4/3.92, 60.8/3.90, 60.8/3.59); a hydroxy group; a dioxymethylene group ( $\delta_C/\delta_H$  101.5/6.00

(d,  $J = 1.5$  Hz) and 5.98 (d,  $J = 1.5$  Hz); an Angeoyl group [ $\delta$  166.9 (C-1')/127.6 (C-2'')/138.8 (CH, C-3''), 5.96 (m, H-3'')/ 15.7 (C-4''), 1.83 (dd,  $J = 3.0, 1.0$  Hz), H-4'')/ 20.1 (C-5''), 1.57 (s, H-5''); and an isovaleryl group [ $\delta_C/\delta_H$  175.9 (C-1')/40.3 (C-2'), 1.74 (H-2'')/26.6 (C-3'), 1.23 and 1.39 (m, 2 H-3'')/ 11.2 (C-4'), 0.75 (t,  $J = 7.5$  Hz, H-4') and 15.1 (H-5'), 0.86 (d,  $J = 7.5$  Hz, H-5'). The abovementioned data showed that compound 1 presented in the dibenzocyclooctadiene skeleton, which was the basic skeleton of compounds from the genus *Schisandra* [3, 4, 5, 6].

In the HMBC spectrum, H-11 interacted with C-9/C-12/C-13, H-9 with C-1', H-4' with C-2'/C-3', and H-5' with C-1'/C-2'/C-3', while dioxymethylene methylene protons at 5.98/6.00 correlated with C-12/C-13 indicating one 2-methylbutyryl group at C-9, and

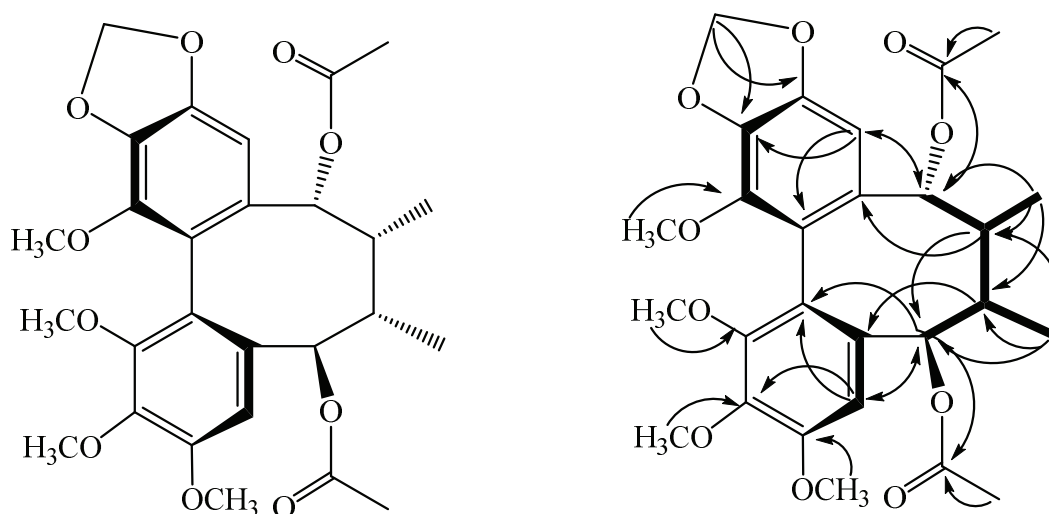
the dioxygenated methylene group attached to C-12 and C-13. In addition, the HMBC correlations from H-4 to C-2/C-3/C-6/C-16, from H-6 to C-1'', from H-4'' to C-2''/C-3'', from H-5'' to C-1''/C-2''/C-3'', from methoxy group at 3.59 to C-1, from methoxy group at 3.90 to C-2, and from methoxy group at 3.92 to C-3, confirmed the location of one angeloyloxy group at C-6 and three methoxy groups at C-1, C-2, and C-3. Detailed analysis of the NMR data showed that compound 1 was quite similar to ananolin J [8].

The COSY spectrum also confirmed the interactions of H-6/H-7/H-8/H-9, H-7/H-18, H-8/H-17 as the structure of ananonin J. The NOESY interactions between H-9 and H-11, and H-6 and H-4 showed that H-9 had  $\beta$  configuration and H-6 had  $\alpha$  configuration. The appearance of NOESY interactions between H-9 and H-7, H-18 and H-6, and H-17 and H-18 showed that two protons H-7 and H-8 both occupied the  $\beta$  position. Based on the above data, compound 1 was determined as ananonin J [8].

**Table 2.** <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectral data for ananolignan F (2).

No.	$\delta_C^{[9]}$	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (J, Hz)	No.	$\delta_C^{[9]}$	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (J, Hz)
1	151.9	151.9	-	15	121.4	121.5	-
2	141.3	141.5	-	16	123.3	123.3	-
3	151.5	151.6	-	17	16.7	16.7	0.96 (d, 7.0)
4	110.6	110.6	6.69 (s)	18	16.8	16.8	0.91 (d, 7.0)
5	131.3	131.3	-	1-OMe	60.1	60.1	3.58 (s)
6	80.9	81.0	5.70 (d, 8.5)	2-OMe	60.6	60.6	3.89 (s)
7	38.0	38.1	2.02 (m)	3-OMe	56.0	56.1	3.89 (s)
8	39.8	39.5	2.12 (m)	14-OMe	59.5	59.5	3.85 (s)
9	79.6	79.6	5.74 (d, 4.5)	OCH <sub>2</sub> O	101.2	101.2	5.97 (d, 1.5) /5.99 (d, 1.5)
10	132.9	132.9	-				
11	102.3	102.4	6.44 (s)	1'	170.0	170.1	-
12	148.6	148.6	-	2'	20.6	20.6	1.57 (s)
13	136.2	136.2	-	1''	170.1	170.1	-
14	141.8	141.8	-	2''	20.9	21.0	1.79 (s)

<sup>a)</sup>CDCl<sub>3</sub>, <sup>b)</sup>125 MHz, <sup>c)</sup>500 MHz. \*The NMR data of ananolignan F [9].



**Figure 2.** Structures and key HMBC and COSY correlations of compound 2.

Compound 2 was obtained as white powder,  $[\alpha]_D^{25} = +75.2$  (c 0.1, MeOH); ECD (0.3 mg/mL in MeOH)  $\theta(\lambda)$ : +3.45(216), -2.17(251). Its molecular formula as  $C_{27}H_{32}O_{10}$  was determined by the HR-ESI-MS ion peak at  $m/z$  539.1889  $[M+Na]^+$  (theoretical calculation for  $[C_{27}H_{32}O_{10}Na]^+$ : 539.1893).

The NMR spectra of compound 2 were similar to those of 1, except the 2-methylbutyryl group and angeloyloxy group, which were replaced by acetyl groups and additional signals due to one methoxy group. The location of acetyl groups at C-6 and C-9 was elucidated by the HMBC correlation from H-9 to C-1', H-2' to C-1', H-6 to C-1'', and H-2'' to C-1''. The location

of the methoxy group at C-14 was elucidated by the HMBC correlation from the methoxy group at 3.85 to C-14. The dioxymethylene group remained attached to C-12 and C-13, and the two acetoxy groups attached to C-6 and C-9. These positions were re-examined by HSQC and HMBC spectra.

Similar to compound 1, the interactions on the NOESY spectrum of H-17/H-18, H-11/H-9, between H-6/H-4, between H-18/H-6 showed H-6 along with two groups 7-CH<sub>3</sub> and 8-CH<sub>3</sub> all had  $\alpha$  configuration, and H-7, H-8, H-9 all had  $\beta$  configuration.

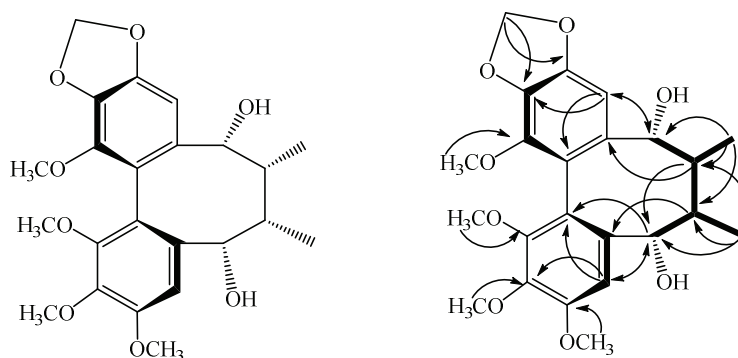
The NMR spectral data of compound 2 was quite similar to ananolignan F. Thus, compound 2 was determined as ananolignan F.



**Table 3.** <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectral data for ananolignan C (3).

No.	$\delta_C^{[9]}$	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (J, Hz)	No.	$\delta_C^{[9]}$	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (J, Hz)
1	151.1	151.1	-	13	135.3	135.4	-
2	140.8	140.9	-	14	141.0	141.0	-
3	153.0	153.0	-	15	117.5	117.6	-
4	106.4	106.5	7.02 (s)	16	119.7	119.8	-
5	135.4	135.5	-	17	9.8	9.8	0.91 (d, 7.5)
6	72.6	72.6	4.71 (d, 2.0)	18	20.3	20.3	1.19 (d, 7.5)
7	43.6	43.7	2.16 (m)	1-OMe	60.6	60.6	3.66 (s)
8	41.6	41.7	2.04 (m)	2-OMe	61.0	61.0	3.90 (s)
9	83.8	83.5	4.58 (d, 10.5)	3-OMe	55.9	56.0	3.91 (s)
10	138.6	138.7	-	14-OMe	59.7	59.7	3.85 (s)
11	102.2	102.2	6.30 (s)	OCH <sub>2</sub> O	101.2	101.2	5.97 (d, 1.5)
12	149.0	149.0	-				5.96 (d, 1.5)

<sup>a)</sup>CDCl<sub>3</sub>, <sup>b)</sup>125 MHz, <sup>c)</sup>500 MHz. \*The NMR data of ananolignan C [9].



**Figure 3.** Structures and key HMBC and COSY correlations of compound 3.

Compound 3 was obtained as white powder,  $n_D^{20} = -27.4$  (c 0.1, MeOH); ECD (0.3 mg/mL in MeOH)  $\theta(\lambda)$ : +3.78(216), -2.18(251); Its molecular formula as C<sub>23</sub>H<sub>28</sub>O<sub>8</sub> was determined by the HR-ESI-MS ion peak at m/z

455.1687 [M+Na]<sup>+</sup> (theoretical calculation for [C<sub>23</sub>H<sub>28</sub>O<sub>8</sub>Na]<sup>+</sup>: 541.2049).

Compound 3 also had spectra similar to those of 1 and 2, which indicated that compound 3 was the dibenzocyclooctadiene lignan compound.

Compared with compound 2, compound 3 has lost the signals of two acetoxy groups at C-6 and C-9, and had all four methoxy groups and two methyl groups presented as doublets, indicating that four methoxy groups must bind to C-1, C-2, C-3, and C-14. Similar to compound 2, C-6 and C-9 were the only two hydroxy groups remaining with proton signals at  $\delta$  4.71 (d,  $J = 2.0\text{Hz}$ ) and 4.58 (d,  $J = 10.5\text{Hz}$ ), where these two protons had HSQC interactions with two carbons at  $\delta$  72.6

and 83.5, respectively. The configuration of protons H-6, H-7, H-8, and H-9 was determined by NOESY spectroscopy showed that they had the  $\beta$  configuration. The NMR spectral data of compound 3 was consistent with the published spectral data of ananolignan C [9].

Thus, compound 3 was determined to be ananolignan C. In addition, the HMBC interactions also further confirmed the structure of this compound [10].

## 2. Results of Inhibitory activity on the NO production in LPS activated RAW264.7 cells of compounds

Many dibenzocyclooctadiene lignans have been reported to exhibit anti-inflammatory activity [3, 4, 5, 6].

**Table 4.** Inhibitory activity on the NO production in LPS activated RAW264.7 cells.

Concentration ( $\mu\text{M}$ )	Compound 1		Compound 2		Compound 3		Dexamethasone (positive control)									
	% NO inhibition		% of cells survived		% NO inhibition		% of cells survived		% NO inhibition		% of cells survived					
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD				
100	98.14	5.13	98.21	1.65	96.54	4.35	98.12	0.22	97.54	4.74	96.00	6.52	89.54	1.96	86.51	2.15
20	23.18	1.34	100.00	2.45	25.43	0.78	99.78	2.32	21.23	0.51	99.98	0.21	52.50	1.65	93.71	1.87
4	13.54	0.99			8.08	0.19			9.04	0.17			39.59	1.56		
0.8	4.67	0.29			4.62	0.27			6.62	0.22			28.24	0.75		
IC <sub>50</sub>	45.24 $\pm$ 1.46		-		41.32 $\pm$ 1.45		-		48.71 $\pm$ 1.34		-		14.20 $\pm$ 0.54		-	

Therefore, compound 1 - 3 were evaluated for anti-inflammatory activity by their ability to inhibit NO production in LPS stimulated RAW 264.7 cells. The results showed that compound 1 - 3 were able to inhibit NO production with IC<sub>50</sub> values of 45.24 ± 1.46, 41.32 ± 1.45, and 48.71 ± 1.34 μM, respectively.

This result was consistent with published reports on inhibitory activity on nitric oxide production on LPS stimulated RAW 264.7 cells of lignans isolated from the genus *Schisandra* [3, 4, 5, 6].

### CONCLUSION

From the methanol extract of *Schisandra cauliflora* roots, three dicycoactadiene lignan compounds were isolated, including ananonin J (1), ananolignan F (2), and ananolignan C (3). Their chemical structures were determined by 1D- and 2D- nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (HR-ESI-MS), and CD spectra.

All three compounds showed the potential of NO inhibition activity production, with IC<sub>50</sub> values of 45.24 ± 1.46, 41.32 ± 1.45, and 48.71 ± 1.34 μM, respectively, compared to that of the positive control of dexamethasone (IC<sub>50</sub> 14.20 ± 0.54 μM).

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