









A New Iridoid Glycoside from Wine-Processed *Corni fructus*

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Abstract: A new iridoid glycoside, cornusglucoside I (**1**), and a new natural product methyl 4-(3',4'-dihydroxyphenyl)-4-oxobutanoate (**2**), together with two known isolated compounds (**3-4**) were obtained from the 30% ethanol extract of the wine-processed *Corni fructus*. Their structures were clarified by spectroscopic analysis and literature data. The absolute configuration of **1** was elucidated by ECD calculation. By evaluating the NO production induced by LPS in RAW 264.7 cells to assess the anti-inflammatory activities of isolated compounds. Among the tested compounds, compounds **3** and **4** exhibited stronger anti-inflammatory activity than the positive drug dexamethasone (6 μ M), which may be potential anti-inflammatory drugs.

Keywords: Iridoid glycoside; wine-processed *Corni fructus*; anti-inflammatory activity. © 2021 ACG Publications. All rights reserved.

1. Introduction

Cornus officinalis is distributed in Shaanxi, Gansu, Jiangxi, Henan and other provinces in China [1]. The fruits of *C. officinalis* have traditionally been used for nourishing the kidneys and liver for thousands of years in China, which was first recorded in Shen Nong's *Materia Medica*. [2]. Previous studies have shown the presence of iridoids, flavonoids, terpenoids, organic acid, polysaccharides and phenylpropanoids in *C. officinalis* [3–6]. Modern pharmacology studies revealed that the extracts and chemical components of *C. officinalis* have extensive biological activity, such as anti-inflammatory, anti-oxidant, anti-diabetes, neuroprotective activities and cardiovascular system activities [7–10]. This traditional Chinese medicine was obtained by steaming the clean pulp with

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yellow millet wine for 4-8 hours, which is the main form of traditional Chinese classical prescription in clinical medication. Modern studies indicated that wine-processed fruit of *C. officinalis* could help enhance the efficacy and reduce acidity compared with the untreated fruit. However, there were few studies on the wine-processed *Corni fructus*.

Modern pharmacology studies have shown that the mechanisms of *C. officinalis* in treating many diseases are related to its anti-inflammatory effects. Inflammation is an adaptive response to injury or harmful stimulation, it is closely related to the development of many diseases [11-13]. To characterize more potential therapeutic agents from the wine-processed *Corni fructus* to prevent inflammation, the chemical compositions were investigated. A new iridoid glycoside, namely cornusglucoside I (**1**), a new natural product methyl 4-(3',4'-dihydroxyphenyl)-4-oxobutanoate (**2**) and two known compounds (**3-4**) were obtained (Fig. 1). And their potential anti-inflammatory activities were determined in our research.

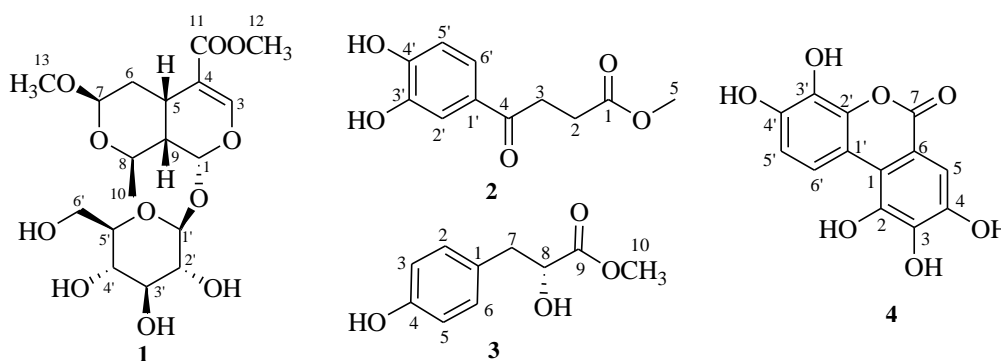


Figure 1. Chemical structures of **1** – **4**.

2. Materials and Methods

2.1. Apparatus and Reagents

Rudolph AP-IV polarimeter (Rudolph, Hackettstown, NJ, USA); EVO 300 spectrometer; UPLC-LTQ orbitrap XL Spectrometer; Nicolet IS 10 spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). QBH LC-52 (Beijing Qingbohua Technology Co., Ltd., Beijing, China). Chirascan CD spectropolarimeter (Applied Photophysics, Leatherhead, Surrey, UK). Bruker Avance III 500-NMR instruments.

2.2. Plant Material

A voucher specimen (No. 2018-0413) of wine-processed *Corni fructus* was kept in the engineering technology research center for comprehensive development and utilization of authentic medicinal materials in Henan province, which were obtained from Zhengzhou Ruilong Co., Ltd. in Henan province, and were identified by Dr. Dai, Henan University of Chinese Medicine.

2.3. Extraction and Isolation

The dried materials (50.0 kg) were extracted with water (500 L × 2, 2 h) at 100°C to give a crude extract, which was separated by D101 macroporous resin with ethanol / water (0:100, 30:70, 70:30, v/v) to afford three parts (Fr. A-Fr. C). Fr. B (3.2 kg) was partitioned with ethyl acetate to afford an EtOAc soluble extract (Fr.B1, 409 g), which was separated into eight fractions (Fr. B1-1 ~ Fr. B1-8) by use of silica gel column (200–300 mesh, CHCl₃/CH₃OH 1:0 to 0:1). Fr. B1-3 was divided by C18 column chromatography with CH₃OH/H₂O to yield Fr. B1-1-1 ~ Fr. B1-1-3. Fr. B1-1-3 was purified

by HPLC with 15% CH₃CN/H₂O to yield compound **2** (8 mg, t_R = 36 min), **3** (7 mg, t_R = 20 min). Fr. B1-5 was isolated using C18 column chromatography with CH₃CN /H₂O and HPLC with 15% CH₃CN/H₂O to give **1** (25 mg, t_R = 30 min), **4** (9 mg, t_R = 18 min).

2.4. Spectral Data

Cornusglucoside I (1): White amorphous powder; [α]_D²⁵ – 39.671 (c 0.042, CH₃OH); IR (KBr) λ_{\max} : 3526, 3301, 2943, 2252, 1630, 1441, 1375, 1073, 1036 cm⁻¹; UV (CH₃OH) λ_{\max} (log ϵ): 233 (1.079) nm; HR-ESI-MS at m/z 443.1528 [M + Na]⁺ (calcd for C₁₈H₂₈O₁₁Na, 443.1529); ¹H NMR (CD₃OD, 500 MHz) and ¹³C NMR (125 MHz, CD₃OD) data (Table 1).

Compound (2): Purple amorphous powder; IR (KBr) λ_{\max} : 3350, 2956, 1730, 1670, 1597, 1440, 1291, 1167 cm⁻¹; UV (MeOH) λ_{\max} (log ϵ): 205 (1.237), 225 (1.176), 269 (0.822), 302 (0.524) nm; HR-ESI-MS at m/z 247.0576 [M + Na]⁺ (calcd for C₁₁H₁₂O₅Na, 247.0582); ¹H NMR (CD₃OD, 500 MHz) and ¹³C NMR (125 MHz, CD₃OD) data (Table 1).

Table 1. ¹H and ¹³C NMR spectra data (500/125 MHz) for **1**, cornusglucoside H and (7 β)-7-O-methylmorrisonide in CD₃OD.

Position	1		Cornusglucoside H		(7 β)-7-O-methylmorrisonide	
	δ_{H}	δ_{C}	LIT $\delta_{\text{H}}^{[15]}$	LIT $\delta_{\text{C}}^{[15]}$	LIT $\delta_{\text{H}}^{[16]}$	LIT $\delta_{\text{C}}^{[16]}$
1	5.62 (1H, d, 3.5)	95.6	5.63 (1H, d, 9.0)	95.6	5.89 (1H, d, 9.1)	95.5
3	7.46 (1H, s)	153.7	7.46 (1H, s)	153.9	7.51 (1H, s)	154.1
4		110.6		110.8		111.7
5	3.18 (1H, m)	25.5	2.84 (1H, dt, 13.2, 4.2)	25.8	3.05 (1H, dt, 12.9, 4.6)	28.5
6	1.64 (1H, m) 2.40 (1H, m)	33.0	1.13 (1H, m) 2.01 (1H, m)	33.2	1.52 (1H, td, 12.9, 3.5) 1.92 (1H, ddd, 12.9, 4.6)	33.1
7	4.38 (1H, d, 7.3)	100.8	4.39 (1H, dd, 9.6, 1.8)	100.9	4.75 (1H, brd, 3.5)	99.8
8	3.75 (1H, m)	69.4	3.73 (1H, m)	69.6	4.29 (1H, 6.9, 2.1)	66.1
9	1.81 (1H, m)	43.1	1.80 (1H, m)	43.2	1.80 (1H, m)	40.5
10	1.38 (3H, d, 6.3)	20.4	1.38 (3H, d, 4.0)	20.6	1.35 (3H, d, 6.9)	18.9
11		168.7		168.9		168.5
12	3.72 (3H, s)	51.7	3.71 (3H, s)	51.8	3.69 (3H, s)	51.4
13	3.42 (3H, s)	56.2	3.42 (3H, s)	56.3	3.35 (3H, s)	54.7
1'	4.66 (1H, d, 7.9)	100.1	4.65 (1H, d, 5.4)	100.3	4.79 (1H, d, 5.4)	99.8
2'	3.21 (1H, m)	74.6	3.19 (1H, m)	74.8	3.22 (1H, dd, 9.4, 7.9)	74.8
3'	3.35 (1H, m)	78.3	3.35 (1H, m)	78.5	3.38 (1H, t, 9.4)	78.0
4'	3.27 (1H, m)	71.5	3.29 (1H, m)	71.7	3.28 (1H, t, 9.4)	71.1
5'	3.38 (1H, m)	77.9	3.37 (1H, m)	78.1	3.37 (1H, m)	78.5
6'	3.68 (1H, dd, 11.9, 5.6) 3.91 (1H, d, 11.9)	62.7	3.68 (1H, m) 3.90 (1H, m)	62.9	3.66 (1H, dd, 12.1, 6.2) 3.89 (1H, dd, 12.1, 6.2)	62.5

Compound (3): White amorphous powder; ¹H NMR (500 MHz, CD₃OD) δ_{H} : 7.04 (1H, d, J = 8.4 Hz, H-3, 5), 6.71 (1H, d, J = 8.4 Hz, H-2, 6), 4.31 (1H, dd, J = 7.5, 5.2 Hz, H-8), 3.69 (3H, s, H-10), 2.96 (1H, dd, J = 13.9, 5.0 Hz, H-7b), 2.83 (1H, dd, J = 13.9, 7.5 Hz, H-7a). ¹³C NMR (125 MHz, CD₃OD) δ_{C} : 175.9 (C-9), 157.2 (C-4), 131.5 (C-3,5), 129.2 (C-1), 116.0 (C-2,6), 73.5 (C-8), 52.3 (C-10), 41.0 (C-7).

Compound (4): Colorless crystal; ¹H NMR (500 MHz, CD₃OD) δ_{H} : 8.45 (1H, d, J = 9.0 Hz, H-6'), 7.38 (1H, s, H-5), 6.76 (1H, d, J = 9.0 Hz, H-5'). ¹³C NMR (125 MHz, CD₃OD) δ_{C} : 163.8 (C-7), 146.8

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(C-4'), 146.5 (C-4), 144.0 (C-2), 142.0 (C-3), 141.0 (C-2'), 133.3 (C-3'), 119.1 (C-6'), 118.5 (C-1), 112.9 (C-1'), 112.4 (C-5'), 112.0 (C-6), 108.1 (C-5).

2.5. Computational Details

The ECD spectra of compound **1** was measured by Applied Photophysics Chirascan CD spectropolarimeter and the energy-minimized conformers was obtained via the Molecular Mechanics field in Spartan 14, and the geometries were further optimized using integral equation formal variable polarization continuum model, without vibration imaginary frequency [14]. The time-dependent density functional theory (TDDFT) method is used to perform the theoretical calculation of the ECD spectrum of the main conformer of **1** at the level of RB3LYP/6-31G (d, p). Gaussian 6.1 was used to calculate the ECD curve. The result of **1** was drawn by SpecDic software and OriginPro 8.

2.6. Determination of RAW 264.7 cells viability *in vitro*

RAW264.7 cells were incubated in a humidified 5% CO₂ atmosphere at 37°C in 96-well plates (8 × 10⁴ cells/well) and treated with different concentrations of isolated compounds (200, 100, 50, 25, 12.5, 6.25, 0 μM). After 24 h, cell viability was measured by CCK-8 method.

2.7. Anti-inflammatory activity *in vitro*

The Griess reaction is used to measure the accumulation of nitrite in the medium. RAW264.7 cells (2.5 × 10⁵ cells/well) were placed on a 96-well microtiter plate and treated with each compound in the presence of LPS (1 μg/mL) for 24 hours. Mixing medium supernatant (50 μl) with Griess reagent (100 μl) (part I: 1% sulfonamide; part II: 0.1% naphthylethylene diamide dihydrochloride and 2% phosphoric acid) at 37°C. After 10 minutes, the absorbance was measured at 540 nm.

3. Results and Discussion

3.1. Structure Elucidation

Cornusglucoside I (**1**) was isolated as a white amorphous powder. The infrared spectrum revealed the hydroxyl (3526 cm⁻¹) and carbonyl (1630 cm⁻¹) groups of **1**. UV spectral data showed three absorption peaks at 233 nm. A HREIMS [M + Na]⁺ peak at *m/z* 443.1528 indicated that the molecular formula of compound **1** was C₁₈H₂₈O₁₁ with 5 sites of unsaturation. The ¹H NMR and ¹³C NMR data displayed characteristic resonances for one methyl [δ_{H} 1.38 (3H, d, *J* = 6.3 Hz, H-10); δ_{C} 20.4 (C-10)], two methylene [δ_{H} 1.64 (1H, m, H-6a), 2.40 (1H, m, H-6b), 3.68 (1H, dd, *J* = 11.9, 5.6 Hz, H-6'a), 3.91 (1H, d, *J* = 11.9 Hz, H-6'b); δ_{C} 33.60 (C-6), 62.7 (C-6'), respectively], three methines [δ_{H} 3.18 (1H, m, H-5), 1.81 (1H, m, H-9), 3.75 (1H, m, H-8); δ_{C} 25.5 (C-5), 43.1 (C-9), 69.4 (C-8), respectively], two methoxy groups [δ_{H} 3.42 (3H, s, H-13), 3.72 (3H, s, H-12); δ_{C} 56.2 (C-13), 51.7 (C-12), respectively], two acetal signals [δ_{H} 5.62 (1H, d, *J* = 3.5 Hz, H-1), 4.38 (1H, d, *J* = 7.3 Hz, H-7); δ_{C} 95.6 (C-1), 100.8 (C-7), respectively], one trisubstituted double bonds [δ_{H} 7.46 (1H, br.s, H-3); δ_{C} 157.3 (C-3), 110.6 (C-4)], one ester carbonyl carbon [δ_{C} 168.7 (C-11)]. The NMR spectrum showed one set of glucose characteristic signals [δ_{H} 3.21 ~ 4.66; δ_{C} 100.1 (C-1'), 74.6 (C-2'), 78.31 (C-3'), 71.51 (C-4'), 77.9 (C-5'), 62.7 (C-6')] (Table 1). The coupling constant (*J* = 7.9 Hz) of the anomeric proton at δ_{H} 4.66 indicated that the glucopyranosyl moiety was in β configuration. These spectroscopic data of **1** was similar to cornusglucoside H and (7 β)-7-*O*-methylmorroneiside, which indicated that **1** may be an iridoid glycoside [15, 16]. The 2D structure of **1** was verified by the HMBC correlations between H-1 and C-5/C-8/C-1'/C-3, H-3 and C-5/C-1/C-4/C-11, H-5 and C-6/C-9/C-8/C-4/C-3, H-7 and C-6/C-5/C-8/C-13, H-10 and C-9/C-8. Furthermore, according to the correlation between H-1 and C-1' in the HMBC spectrum, it is judged that the C-1' is connected to C-1 position, and the planar structure is

determined to be the same as cornusglucoside H and (7 β)-7-*O*-methylmorroneiside [15, 16]. The relative configuration of **1** was established by a NOESY experiment (Fig. 2). The NOE correlations

from H-9 to H-1/H-5/H₃-10, and from H₃-13 to H₃-10 indicated their cofacial orientation, and H-7, H-8 were on the other side. And the optical rotation value of **1** was $[\alpha]_{\text{D}}^{25} - 39.671$ (c 0.042, CH₃OH), which was different from that of cornusglucoside H $[\alpha]_{\text{D}}^{20} - 165.45$ (c 0.04, CH₃OH) and (7 β)-7-*O*-methylmorroneiside $[\alpha]_{\text{D}}^{20} - 125$ (c 0.083, CH₃OH) [15, 16]. The correlations of NOESY spectrum confirmed that its relative configuration, which is different from that of cornusglucoside H and (7 β)-7-*O*-methylmorroneiside.

In order to further verify the absolute configuration of β -glucose, acid hydrolysis was carried out according to the method of literature, and the optical rotation value of β -glucose was $[\alpha]_{\text{D}}^{25} = + 11$ (c 0.07, MeOH), which determined the structure of β -D-glucose.

The calculated ECD spectrum of **1** showed a positive Cotton effect at 250 nm and a negative Cotton effect at 225 nm (Fig. 3), which matched well with that of the experimental one. Thus, the absolute configuration of **1** was 1*R*, 5*S*, 7*R*, 8*R*, 9*S*.

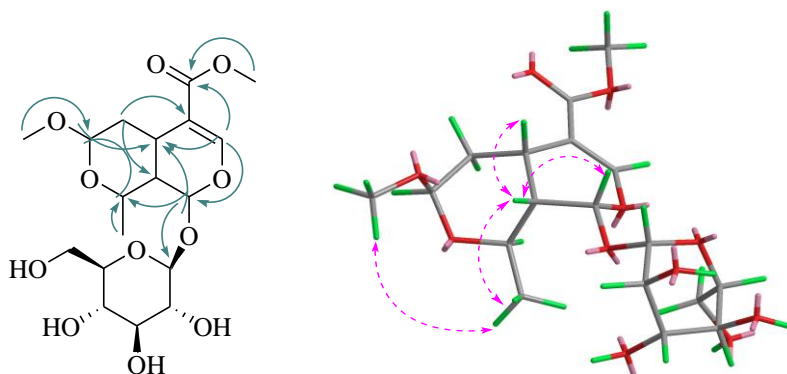


Figure 2. HMBC (—) and NOESY (---) correlations of compound **1**.

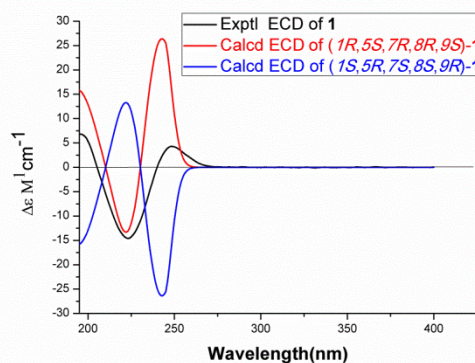


Figure 3. Comparison of the experimental and calculated ECD spectra of compound **1**

Compound **2** was obtained as purple amorphous powder and gave a $[M + Na]^+$ peak at m/z 247.0576 in the HRESIMS for a molecular formula of C₁₁H₁₂O₅Na, requiring 6 sites of unsaturation. The IR spectrum (3350, 1730 cm⁻¹) showed the presence of hydroxyl and carbonyl groups. UV spectral data showed three absorption peaks at 205, 225, 269, 302 nm. The ¹H NMR data (Table 1) displayed characteristic resonances for one ABX trisubstituted phenyl signals [δ_{H} 6.83 (1H, d, J = 8.0 Hz, H-5'), 7.42 (1H, s, H-2'), 7.45 (1H, d, J = 8.0 Hz, H-6')], two methylene [δ_{H} 2.67 (2H, t, J = 6.2 Hz, H-2), 3.25 (2H, t, J = 6.2 Hz, H-3)], one methoxy signal [δ_{H} 3.67 (3H, s, H-5)]. The ¹³C NMR spectrum showed one set of phenyl signals [δ_{C} 115.8 (C-2'), 115.9 (C-5'), 122.9 (C-6'), 130.2 (C-1'), 146.5 (C-3'), 152.3 (C-4')], one ester carbonyl carbon [δ_{C} 175.4 (C-1)], one ketocarbonyl carbon [δ_{C} 199.1 (C-4)], one methoxy carbon [δ_{C} 52.2 (C-5)] and other two sp³ carbon [δ_{C} 29.1 (C-2), 33.8 (C-3)]. The HMBC correlations from H-2 to C-1/C-3/C-4, H-3 and C-1/C-2/C-4, H-5 and C-1, H-2' and C-4/C-4'/C-6', H-5'to C-1'/C-3', and H-6' to C-4/C-2'/C-4' (Fig. 4). The ¹H and ¹³C NMR spectroscopic

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data of **2** were comparable with those of methyl 4-(3',4'-dihydroxyphenyl)-4-oxobutanoate. Analysis of the NMR data as well as the HMBC correlations clarified the elucidation for the structure of **2**, which is same as a synthetic compound reported in the literature [17]. Therefore, we determined that compound **2** is a new natural product, namely methyl 4-(3',4'-dihydroxyphenyl)-4-oxobutanoate.

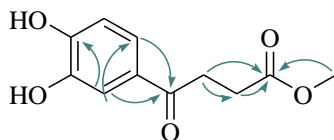


Figure 4. HMBC correlations (\curvearrowright) of compound **2**

Compound **3** was obtained as White amorphous powder. The ^1H NMR and ^{13}C NMR data displayed characteristic resonances for *p*-disubstituted phenyl signals [δ_{H} 7.04 (1H, d, $J = 8.4$ Hz, H-3, 5), 6.71 (1H, d, $J = 8.4$ Hz, H-2, 6); δ_{C} 129.2 (C-1), 116.0 (C-2,6), 131.5 (C-3,5), 157.2 (C-4), respectively], one oxygenated methine [δ_{H} 4.31 (1H, dd, $J = 7.5, 5.2$ Hz, H-8); δ_{C} 73.5 (C-8)], one one methoxy signal [δ_{H} 3.69 (3H, s, H-10); δ_{C} 52.3 (C-10)], one methylene [δ_{H} 2.96 (1H, dd, $J = 13.9, 5.0$ Hz, H-7b), 2.83 (1H, dd, $J = 13.9, 7.5$ Hz, H-7a); δ_{C} 41.0 (C-7)], and one ester carbonyl carbon [δ_{C} 175.9 (C-9)]. Compounds **3** was determined as methyl *p*-hydroxyphenyllactate based on the ^1H and ^{13}C NMR data [18].

Compound **4** was obtained as Colorless crystal. The ^1H NMR and ^{13}C NMR data displayed characteristic resonances for two phenyl signals [δ_{H} 7.38 (1H, s, H-5), 6.76 (1H, d, $J = 9.0$ Hz, H-5'), 8.45 (1H, d, $J = 9.0$ Hz, H-6'); δ_{C} : 118.5 (C-1), 144.0 (C-2), 142.0 (C-3), 146.5 (C-4), 108.1 (C-5), 112.0 (C-6), 112.9 (C-1'), 141.0 (C-2'), 133.3 (C-3'), 146.8 (C-4'), 112.4 (C-5'), 119.1 (C-6')], and one ester carbonyl carbon [δ_{C} 163.8 (C-7)]. Compounds **4** was determined as 3,4,8,9,10-Pentahydroxydibenzo[b,d]pyran-6-one based on the ^1H and ^{13}C NMR data [19].

3.2. Biological Activities

RAW264.7 viability: The *in vitro* cytotoxicity of compounds (**1-4**) on RAW264.7 cells were evaluated by CCK-8 assay. As shown in Fig. S18. Compound **1** showed no cytotoxic activity toward RAW264.7. Compound **2** showed very weak cytotoxic activity that IC_{50} value was greater than 200 μM . Compound **3** and **4** have different levels of cytotoxic activity toward RAW264.7 with IC_{50} values of 17.2 μM and 13.5 μM . According to the result of cells viability assay, we selected the appropriate dosage concentration that make the cell survival rate greater than 90%, and conduct the anti-inflammatory assay.

The anti-inflammatory activities *in vitro* of the compound **1** (6.25, 50, 200 μM) and compounds **2**, **3**, **4** (1.5, 3, 6 μM) were assayed by assessing LPS-induced NO production. Significantly, compounds **3** and **4** (1.5, 3, 6 μM) have the better anti-inflammatory activity than positive control dexamethasone (6 μM).

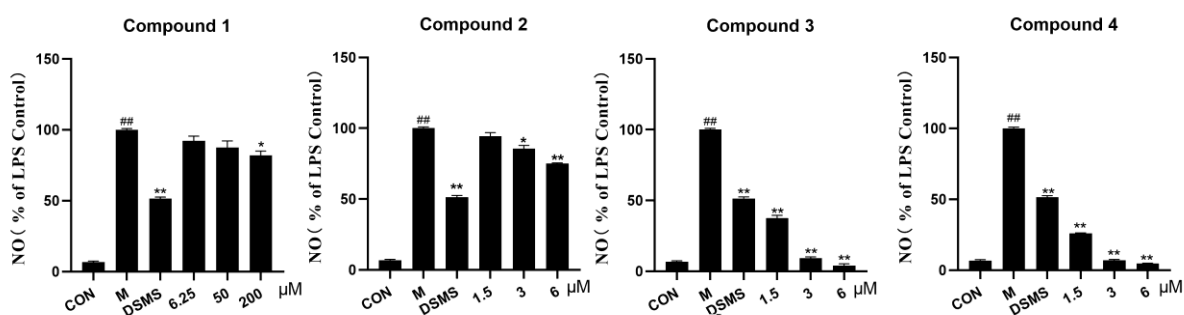


Figure 5. The effect of compounds **1-4** on the level of NO in RAW264.7 cells induced by LPS

($\bar{x} \pm s$, $n = 3$). Positive drug: dexamethasone (DSMS); Compare with control $^{##} P < 0.001$; Compare with model $^{*} P < 0.05$, $^{**} P < 0.001$.

4. Conclusion

In present study, systematic chemical research was carried out and resulted in the separation of a new iridoid glycoside (**1**), together with a new natural product (**2**) and two known compounds (**3-4**) from the ethyl acetate layer of wine-processed Corni fructus. The literature showed that iridoids and organic acids have anti-inflammatory activity. All compounds have been subjected to anti-inflammatory experiments *in vitro*. As the results shown, **1** and **2** showed very weak anti-inflammatory activity, and compounds **3** and **4** have more effective activities than the positive drug dexamethasone (6 μ M). **3** is an inhibitor of cell growth and proliferation and an endogenous ligand for nuclear type-II binding sites [20]. There are few reports on its anti-inflammatory activity in the literature. Compound **4** has potential anti-inflammatory activity as an ellagic compound [21]. This research has enriched the information on the chemical composition of wine-processed Corni fructus, which is conducive to a better understanding of the medicinal characteristics of this traditional Chinese medicine.

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Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/records-of-natural-products>

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