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 μM), which may be potential anti-inflammatory drugs.

1. Introduction

Cornus officinalis is distributed in 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, poly-saccharides 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 (Figure 1). And their potential anti-inflammatory activities were determined in our research.
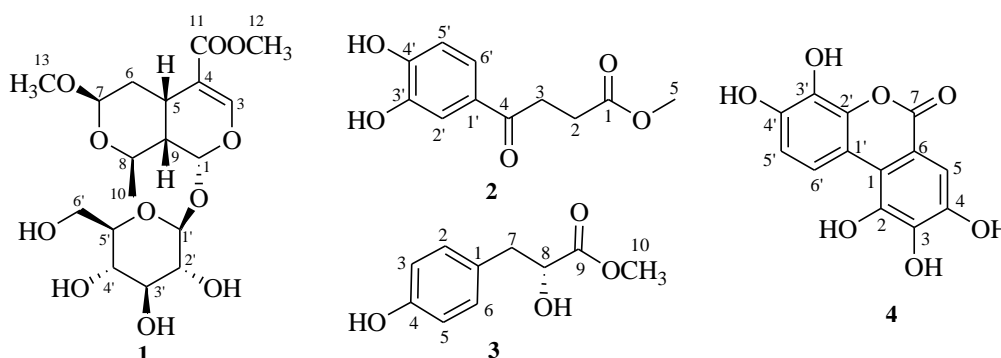

Figure 1. Chemical structures of **1** – **4**

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, CHCl$_3$/CH$_3$OH 1:0 to 0:1). Fr. B1-3 was divided by C18 column chromatography with CH$_3$OH/H$_2$O to yield Fr. B1-1-1 ~ Fr. B1-1-3. Fr. B1-1-3 was purified by HPLC with 15% CH$_3$CN/H$_2$O 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 CH_3CN /H_2O and HPLC with 15% CH_3CN/H_2O 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; $[\alpha]_D^{25} -39.671$ (*c* 0.042, CH_3OH); IR (KBr) λ_{max}: 3526, 3301, 2943, 2252, 1630, 1441, 1375, 1073, 1036 cm^{-1}; UV (CH_3OH) λ_{max} (log ε): 233 (1.079) nm; HR-ESI-MS at *m/z* 443.1528 $[M + Na]^+$ (calcd for $C_{18}H_{28}O_{11}Na$, 443.1529); ^1H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (125 MHz, CD_3OD) 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 $C_{11}H_{12}O_5Na$, 247.0582); ^1H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (125 MHz, CD_3OD) data (Table 1).

Table 1. ^1H and ^{13}C NMR spectra data (500/125 MHz) for **1**, cornusglucoside H and (7*β*)-7-*O*-methylmorroniside in CD_3OD.

Position	1		Cornusglucoside H		(7*β*)-7-*O*-methylmorroniside	
	δ_H	δ_C	LIT $\delta_H^{[15]}$	LIT $\delta_C^{[15]}$	LIT $\delta_H^{[16]}$	LIT $\delta_C^{[16]}$
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, CD_3OD) 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). ^{13}C NMR (125 MHz, CD_3OD) 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, CD_3OD) 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'). ^{13}C NMR (125 MHz, CD_3OD) δ_C: 163.8 (C-7), 146.8 (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).

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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% CO_2 atmosphere at 37°C in 96-well plates (8 $\times 10^4$ 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 (2.5×10^5 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 $C_{18}H_{28}O_{11}$ with 5 sites of unsaturation. The ^{1}H NMR and ^{13}C 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, 5.6Hz, 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*-methylmorroniside, 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*-methylmorroniside [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/H$_3$-10, and from H$_3$-13 to H$_3$-10 indicated their cofacial orientation, and H-7, H-8 were on the other side. And the optical rotation value of **1** was [α]$_D^{25}$ − 39.671 (*c* 0.042, CH$_3$OH),

which was different from that of cornusglucoside H $[\alpha]_D^{20}$ − 165.45 (*c* 0.04, CH$_3$OH) and (7β)-7-*O*-methylmorroniside $[\alpha]_D^{20}$ − 125 (*c* 0.083, CH$_3$OH) [15, 16]. The correlations of NOESY spectrum confirmed that its relative configuration, which is different from that of cornusglucoside H and (7β)-7-*O*-methylmorroniside.

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 $[\alpha]_D^{25}$ = + 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*.
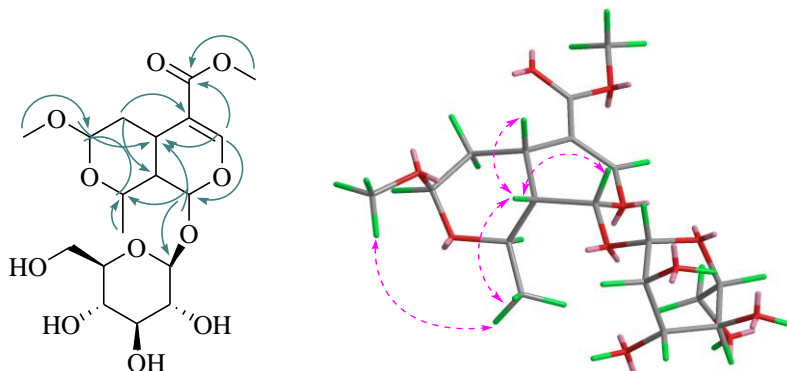

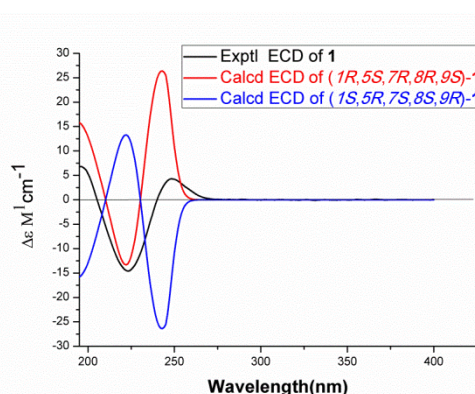**Figure 2**. HMBC (⌒➔) and NOESY (⌁➔) correlations of compound **1**.

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 C$_{11}$H$_{12}$O$_5$Na, 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 ^{1}H 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 ^{13}C 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 sp^3 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 ^{1}H and ^{13}C NMR spectroscopic 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**,

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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.
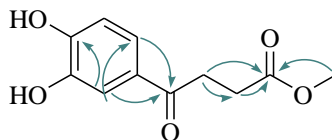

Figure 4. HMBC correlations ( ) of compound **2**

Compound **3** was obtained as White amorphous powder. The ^{1}H 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 ^{1}H and ^{13}C NMR data [18].

Compound **4** was obtained as Colorless crystal. The ^{1}H NMR and ^{13}C NMR date 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 ^{1}H 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).
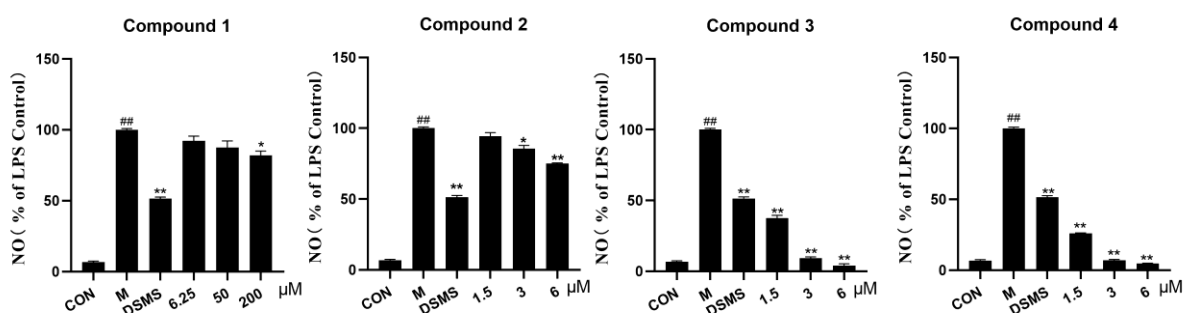

Figure 5. The effect of compounds **1-4** on the level of NO in RAW264.7 cells induced by LPS (x±s, n = 3). Positive drug: dexamethasone (DSMS); Compare with control $^{\#\#}$ $P < 0.001$; Compare with model * $P < 0.05$, ** $P < 0.001$.

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 μM). **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.

Acknowledgments

Supporting Information

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

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