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Aldose Reductase Inhibitory Alkaloids from *Corydalis ternata*

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Abstract – A methanolic extract of *Corydalis ternata* having aldose reductase inhibitory activity was examined as a possible aldose reductase (ALR2) inhibitor, a key enzyme involved in diabetic complications. Seven alkaloids, tetrahydrocoptisine (**1**), corydaline (**2**), tetrahydropalmatine (**3**), isocorybulbine (**4**), corybulbine (**5**), dehydrocorydaline (**6**), and *N*-methyltetrahydroberbinium (**7**) were isolated from $CHCl_3$ fraction of *C. ternata* methanol extract. Among them, compounds **1**, **5**, and **7** exhibited 5.04 ± 1.97%, 5.00 ± 1.26%, and 1.80 ± 2.33% inhibitions, respectively at 40 μM. The activities of the single compounds were not comparable to that of the whole extract, suggesting that the whole combination of each single compound was responsible for the activity of the extract as shown in many cases of natural medicines. Even though this is the second report on aldose reductase inhibition activity of *C. ternata*, recombinant human aldose reductase was employed in this study unlike in the previous report. Furthermore, the aldose reductase inhibitory activities of isocorybulbine, corybulbine, and *N*-methyltetrahydroberbinium, to the best of our knowledge, were evaluated for the first time in this study. These results suggest a use of the extract of *C. ternata* for ameliorating diabetic complications.
Keywords - *Corydalis ternata*, Aldose reductase inhibition activity, Isoquinoline alkaloids

Introduction

Corydalis tuber has been used for an analgesic and an anti-gastric ulcers as a traditional Korean medicine.[1] Some constituents from Corydalis tuber have been reported to have anti-cholinesterase, anti-inflammatory, antihypertensive, and analgesic activities.[2-4] Particularly, it was reported to deplete the levels of amygdaloid dopamine, having neuroprotective effects in heat-stroke rats.[5,6] Corydalis tuber consists of the tubers of many *Corydalis* species and *Corydalis ternata* is the main species used for Corydalis tuber in Korea. Tubers of a variety of *C.* species, including *C. stenantha*, *C. thalictrifolia*, *C. racemosa*, and *C. pallidoma*, etc. were reported to have been used for the treatment of eye diseases.[7] Main chemical constituents of *C. ternata* are reported to be isoquinoline alkaloids, including berberine and coptisine.[1]

Aldose reductase 2 (ALR2) is known to be a rate-limiting enzyme to catalyze the conversion of excess D-glucose into D-sorbitol,[8,9] suggesting that it is involved in the development of diabetic complications.[10,11] These metabolic abnormalities have been reported to play important roles not only in cataract formation[12] but also in the pathogenesis of diabetic complications such as neuropathy.[13,14] For this reason, discovery of ALR2 inhibitors has been considerable biomolecular targets for the treatment of diabetic complications. Currently, four different types of chemicals have been developed as ALR2 inhibitors.[15] However, most of the synthetic compounds have been reported to have unacceptable side effects.[16,17] A number of natural ALR2 inhibitors, especially flavonoids, have also been reported together with their structure-activity relationships.[18-20] The inhibition spectrum of natural inhibitors are reported to be extensive because the source for ALR2 are bovine, rat, and recombinant ALR2. A well-known ALR2 inhibitor, quercitrin is still two times less effective than a commercial synthetic ALR2 inhibitor, epalrestat on rat lens ALR2.[18] Thus, there is still an urgent need for new ALR2 inhibitors.

As a part of our continuing search for aldose reductase inhibitory constituents from Korean medicinal plants, we investigated that the MeOH extract of Corydalis tuber showed considerable inhibitory activity against aldose reductase in screening procedures. Although there have

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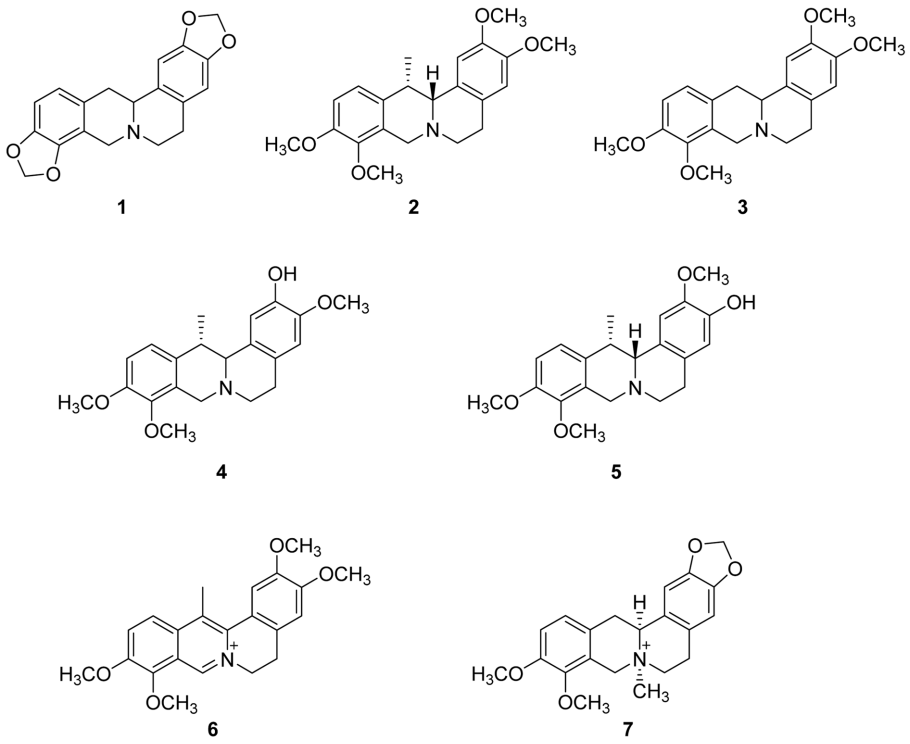

Fig. 1. Chemical structures of the compounds isolated from *C. ternata*.

been a study for aldose reductase inhibitory constituents of congeneric plants,[21] the bioactive constituents of this plant have seldom been investigated. The chemical investigation of the MeOH extracts of Corydalis tuber resulted in the isolation of seven isoquinoline-type alkaloids (**1** - **7**) (Fig. 1) based on bioassay-guided fractionation. Herein, we describe the isolation of the alkaloids and their aldose reductase inhibitory activities.

Experimental

General experimental procedures – NMR spectra were recorded with Varian's standard pulse program of Varian VNS spectrometer at 300 MHz and 500 MHz. EI-MS spectra were recorded with Micromass spectrum (AUTOSPEC, UK). TLC was done using Kieselgel 60F254 (Merck) and RP-18 (Whatman). Column chromatography was done using silica gel (70 - 230 mesh, Merck) and Sephadex LH-20 (Merck).

Plant materials – The tubers of *C. ternata* were provided by Dongguk University (Republic of Korea). A voucher specimen (No. NPC-12-04) was placed in the Pharmacognosy/Natural Products Chemistry Laboratory of College of Pharmacy, Duksung Women's University.

Extraction and isolation – Dried *C. ternata* root (1 kg) underwent extraction with MeOH, and extracts were successively partitioned with *n*-hexane, chloroform ($CHCl_3$), and ethyl acetate (EtOAc). The $CHCl_3$ fraction (17.8 g) was subjected to silica gel column chromatography elution with a chloroform and methanol gradient system (80:1→1:1), yielding 18 fractions (Fr. 1 - Fr. 18). Fraction 7 was subjected to Sephadex LH-20 column chromatography with MeOH to yield compound **1**. Fraction 2 was crystallized with MeOH to yield compound **2**. Fraction 10 was separated by silica gel column chromatography with the elution of cyclohexane: EtOAc : diethylamine (50:1: 0.1 → 1:5:0.6) to give 20 subfractions (Fr. 10-1 ~ Fr. 10-20). Fraction 10-3 was crystallized with MeOH to yield compound **3**. Fractions 10 - 5 and 10 - 19 were further subjected to silica gel column chromatography with the elution of cyclohexane: EtOAc : diethylamine to lead to compounds **4** and **5**, respectively. Fraction 13 was subjected to sephadex LH-20 column chromatography with the elution of MeOH to give compound **6**. Fraction 18 was subjected to silica gel column chromatography with the elution of cyclohexane: EtOAc : diethylamine to lead to compound **7**.

Tetrahydrocoptisine (1) – White powders. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.64 (2H, m, H-5$_{ax}$ and H-6$_{ax}$), 2.79 (1H, m, H-13$_{ax}$), 3.12 (2H, m, H-5$_{eq}$ and H-6$_{eq}$), 3.23 (1H, dd, J = 16, 3.6 Hz, H-13$_{eq}$), 3.54 (1H, d, J = 15 Hz, H-8$_{eq}$), 3.59 (1H, d, J = 3.2 Hz, H-13$_{ax}$), 4.08 (1H, d, J = 15

Hz, H-8$_{ax}$), 5.92 (2H, s, 2,3-OCH$_2$O-), 5.95 (2H, s, 9,10-OCH$_2$O-), 6.59 (1H, s, H-4), 6.63 (1H, d, J = 7.8, H-11), 6.68 (1H, d, J = 7.8 Hz, H-12), 6.72 (1H, s, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 29.5 (C-5), 36.4 (C-13), 51.2 (C-6), 52.8 (C-8), 59.7 (C-13a), 100.8 (2,3-O<u>C</u>H$_2$O-), 101.0 (9,10-O<u>C</u>H$_2$O-), 105.5 (C-1), 106.8 (C-11), 108.4 (C-4), 116.6 (C-8a), 121.0 (C-12), 127.7 (C-4a), 128.4 (C-12a), 130.5 (C-4a), 143.3 (C-10), 145.0 (C-2), 146.0 (C-3), 146.2 (C-9); EI-MS *m/z*, 323.1 [M]$^+$.

Corydaline (2) – White powders. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 0.95 (3H, d, J = 6.9 Hz, H$_3$-14), 2.60 (2H, m, H-5$_{ax}$ and H-6$_{ax}$), 3.11 (2H, m, H-5$_{eq}$ and H-6$_{eq}$), 3.23 (1H, m, H-13$_{eq}$), 3.50 (1H, d, J = 15 Hz, H-8$_{eq}$), 3.69 (1H, d, J = 2.3 Hz, H-13a), 3.88 (12H, m, 2,3,9,10-OCH$_3$), 4.20 (1H, d, J = 15 Hz, H-8$_{ax}$), 6.61 (1H, s, H-4), 6.69 (1H, s, H-1), 6.82 (1H, d, J = 8.4 Hz, H-11), 6.90 (1H, d, J = 8.4, H-12); ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 18.2 (C-14), 29.2 (C-5), 38.1 (C-13), 51.3 (C-6), 54.3 (C-8), 55.7 (2,10-OCH$_3$), 56.0 (3-OCH$_3$), 60.0 (9-OCH$_3$), 62.9 (C-13a), 108.6 (C-1), 110.8 (C-11), 111.0 (C-4), 123.9 (C-12), 128.2 (C-14a), 128.3 (C-4a, C-8a), 134.8 (C-12a), 144.7 (C-10), 147.0 (C-2), 147.3 (C-3), 149.9 (C-9); EI-MS *m/z*, 369.4 [M]$^+$.

Tetrahydropalmatine (3) – ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 2.59 (1H, m, H-5$_{ax}$), 2.65 (1H, m, H-6$_{ax}$), 2.79 (1H, dd, J = 15, 11 Hz, H-13$_{ax}$), 3.11 (1H, m, H-5$_{eq}$), 3.17 (1H, m, H-6$_{eq}$), 3.23 (1H, dd, J = 15, 3.6 Hz, H-13$_{eq}$), 3.49 (1H, dd, J = 11, 3.6 Hz, C-13a), 3.50 (1H, d, J = 15 Hz, C-8$_{eq}$), 3.80 (3H, s, 10-OCH$_3$), 3.82 (3H, s, 9-OCH$_3$), 3.83 (3H, s, 3-OCH$_3$), 3.85 (3H, s, 2-OCH$_3$), 4.21 (1H, d, J = 15 Hz, H-8$_{ax}$), 6.58 (1H, s, H-4), 6.70 (1H, s, H-1), 6.75 (1H, d, J = 8.3 Hz, H-11), 6.84 (1H, d, J = 8.3 Hz, H-12); ^{13}C-NMR(75 MHz, $CDCl_3$) : δ 28.9 (C-5), 36.2 (C-13), 51.3 (C-6), 53.8 (C-8), 55.6 (3-OCH$_3$), 55.8 (2,10-OCH$_3$), 59.1 (C-13a), 59.9 (9-OCH$_3$), 108.3 (C-1), 110.6 (C-11), 111.0 (C-4), 123.6 (C-12), 126.5 (C-4a), 127.5 (C-8), 128.4 (C-12), 129.4 (C-14a), 144.7 (C-10), 147.1 (C-2), 147.1 (C-3), 149.9 (C-9); EI-MS *m/z*, 355.4 [M]$^+$.

Isocorybulbine (4) – Yellow powders. ^{1}H-NMR (500 MHz, Pyridine-d_5) δ : 1.18 (3H, d, J = 6.5 Hz, H-14), 2.52 (2H, m, H-5$_{ax}$ and H-6$_{ax}$), 2.53 (1H, m, H-5$_{eq}$), 3.08 (1H, m, H-6$_{eq}$), 3.11 (1H, qd, J = 6.5, 3.3 Hz, H-13), 3.56–3.41 (2H, m, H-8$_{eq}$, 13a), 3.72 (3H, s, OCH$_3$), 3.80 (3H, s, OCH$_3$), 3.85 (3H, s, OCH$_3$), 4.35 (1H, d, J = 15 Hz, H-8$_{ax}$), 6.91 (1H, d, J = 8.0 Hz, H-11), 6.97 (1H, s, H-4), 6.98 (1H, d, J = 8.0 Hz, H-12), 7.00 (1H, s, H-1); ^{13}C-NMR (75 MHz, Pyridine-d_5) : δ 18.9 (C-14), 30.4 (C-5), 38.4 (C-13), 52.6 (C-6), 55.5 (C-8), 56.1 (OCH$_3$), 56.2 (OCH$_3$), 60.5 (OCH$_3$), 63.3 (C-13a), 109.8 (C-1), 111.2 (C-11), 111.3 (C-4), 124.1 (C-12), 129.0 (C-4a), 129.3 (C-8a), 129.5 (C-12a), 135.3 (C-13a), 145.0 (C-10), 147.3 (C-9), 148.8 (C-3), 150.6 (C-2); EI-MS *m/z*, 355.4 [M]$^+$.

Corybulbine (5) – yellow powders. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 0.93 (3H, d, J = 6.5 Hz, H-14), 2.56 (1H, m, H-5$_{ax}$), 3.02 (1H, m, H-6$_{ax}$), 3.13 (1H, m, H-5$_{eq}$), 3.18 (1H, qd, J = 6.5, 3.3 Hz, H-13), 3.47 (2H, d, J = 15 Hz, H-8$_{eq}$ and H-13a), 3.66 (1H, br s, H-6$_{eq}$), 3.84 (6H, s, 2 × OCH$_3$), 3.86 (3H, s, OCH$_3$), 4.12 (1H, d, J = 15 Hz, H-8$_{ax}$), 6.64 (1H, s, H-4), 6.65 (1H, s, H-1), 6.80 (1H, d, J = 8.0 Hz, H-11), 6.88 (1H, J = 8.0 Hz, H-12); ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 18.4 (C-14), 29.2 (C-5), 38.5 (C-13), 51.4 (C-6), 54.5 (C-8), 55.9 (OCH$_3$), 56.2 (OCH$_3$), 60.2 (OCH$_3$), 63.2 (C-13a), 108.0 (C-1), 111.0 (C-11), 114.1 (C-4), 124.0 (C-12), 128.1 (C-4a), 128.6 (C-8a), 129.3 (C-12a), 135.0 (C-13a), 143.7 (C-10), 144.9 (C-9), 145.5 (C-3), 150.1 (C-2); EI-MS *m/z*, 355.4 [M]$^+$.

Dehydrocorydaline (6) – Yellow powders. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 9.82 (1H, s, H-8), 8.17 (1H, d, J = 9.0 Hz, H-12), 8.05 (1H, d, J = 9.0 Hz, H-11), 7.56 (1H, s, H-1), 7.06 (1H, s, H-4), 4.94 (2H, t, J = 6.5 Hz, H-6), 4.12 (6H, s, OMe), 4.07 (3H, s, OMe), 3.91 (3H, s, OMe), 3.20 (2H, m, H-5), 2.50 (3H, s, 13-Me); ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 26.0 (C-5), 39.8 (13-Me), 55.6 (C-6), 56.0 (2, 10-OMe), 57.2 (3-OMe), 61.9 (9-OMe), 111.6 (C-1), 112.4 (C-4), 119.1 (C-8a), 119.5 (C-13), 121.4 (C-14a), 123.4 (C-12), 127.0 (C-11), 128.5 (C-12a), 133.3 (C-4a), 137.9 (C-13a), 143.8 (C-10), 145.2 (C-8), 146.5 (C-2), 150.1(C-3), 150.8 (C-9); EI-MS *m/z*, 348.4 [M]$^+$.

***N*-methyltetrahydroberbinium (7)** – Colorless crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 3.09 (1H, dd, J = 18, 10 Hz, H-13α), 3.16 (2H, m, H$_2$-5), 3.27 (3H, s, *N*-CH$_3$), 3.43 (1H, dd, J = 18, 5 Hz, H-13β), 3.69 (1H, m, H-6α), 3.78 (1H, m, H-6β), 3.80 (1H, s, 10-OCH$_3$), 3.81 (1H, s, 9-OCH$_3$), 4.84 (1H, d, J = 15.5 Hz, H-8β), 4.9 (1H, m, H-14), 4.95 (1H, d, J = 15 Hz, H-8α), 6.02 (1H, -OCH$_2$O), 6.03 (1H, -OCH$_2$O), 6.88 (1H, s, H-4), 6.95 (1H, s, H-1), 6.97 (1H, d, J = 8.3 Hz, H-12), 7.09 (1H, d, J = 8.3 Hz, H-11); ^{13}C-NMR (75 MHz, DMSO-d_6) δ : 22.6 (C-5), 33.7 (C-13), 50.2 (-NCH$_3$), 52.1 (C-6), 56.7 (10-OCH$_3$), 59.1 (C-8), 61.1 (9-OCH$_3$), 65.0 (C-13a), 102.0 (-OCH$_2$O), 107.7 (C-1), 109.8 (C-4), 114.2 (C-11), 120.1 (C-8a), 122.1 (C-4a), 122.3 (C-12a), 124.0 (C-12), 125.2 (C-14a), 145.6 (C-9), 147.6 (C-2), 148.9 (C-3), 151.6 (C-10); EI-MS *m/z*, 354.1 [M]$^+$.

Recombinant human aldose reductase 2 (rhALR2) inhibitory activity assay – The activities of rhALR2 were evaluated spectrophotometrically by measuring the decreased absorption of NADPH at 340 nm over a 5-min period with DL-glyceraldehyde as a substrate.[22] Each 1.0 mL cuvette contained 0.087 U of enzyme, 0.1 M sodium

Table 1. Effects of methanolic extracts and fractions of Corydalis tuber on rhALR2

Ex./Frs.	Conc. (μg/ml)	Inhibition[1] (%)
MeOH ex.	100	75.4 ± 5.2
	50	32.5 ± 2.1
	25	11.4 ± 1.3
$CHCl_3$ fr.	100	63.4 ± 4.2
	50	25.8 ± 3.4
	25	8.7 ± 1.1
EtOAc fr.	100	7.5 ± 1.6
	50	–[2]
	25	–[2]
Water fr.	100	–[2]

[1]Inhibitory rate was calculated as a percentage relative to the control value and expressed as the mean ± standard deviation of triplicate experiments.
[2]Inhibition (%) was less than 1%.

Table 2. Inhibitory effect of compounds isolated from *C. ternata* on rhALR2 activity

Compounds	Conc. (μM)	Inhibition[2] (%)	IC_{50}[3] (μM)
TMG[1]	40	72.62 ± 0.10	10.06
	20	62.56 ± 1.28	
	10	51.38 ± 1.43	
	5	36.74 ± 2.20	
1	40	5.04 ± 1.97	>40
2	40	–[4]	>40
3	40	–[4]	>40
4	40	–[4]	>40
5	40	5.00 ± 1.26	>40
6	40	–[4]	>40
7	40	1.80 ± 2.33	>40

[1]Tetramethylene glutaric acid (TMG) was used as a positive control.
[2]Inhibitory rate was calculated as a percentage relative to the control value and expressed as the mean ± standard deviation of triplicate experiments.
[3]The concentration of each test sample resulting in 50% inhibition of activity (IC_{50}) was estimated from the least-squares regression line of the logarithmic concentration plotted against inhibitory activity.
[4]Inhibition (%) was less than 1%.

phosphate buffer (pH 6.2), and 0.3 mM NADPH, with or without 10 mM substrate and inhibitor. One U of enzyme was defined as the amount of enzyme required to reduce 1 μmol of NADPH in 1 mL of reaction solution per min.

Result and Discussion

The methanol extract of *C. ternata* and $CHCl_3$, EtOAc, and water-soluble fractions of the extract were evaluated for ALR2 inhibitory activity using DL-glyceraldehyde as a substrate, of which results were summarized in Table 1. The methanol extract and $CHCl_3$-soluble fraction of the extract exhibited strong inhibitory activities against rhALR2, therefore the $CHCl_3$-soluble fraction was further investigated to elucidate bioactive compounds of the fraction. Seven compounds were ultimately isolated from the $CHCl_3$ fraction. They were identified as tetrahydrocoptisine (**1**), corydaline (**2**), tetrahydropalmatine (**3**), isocorybulbine (**4**), corybulbine (**5**), dehydrocorydaline (**6**), and N-methyltetrahydroberbinium (**7**) by spectral analysis and direct comparison with authentic compounds as shown in Fig. 1.[23-26] Seven alkaloids isolated from the $CHCl_3$-soluble fraction were also evaluated for the inhibitory activity on rhALR2 shown in Table 2. Among the isolated compounds, compounds **1**, **5**, and **7** exhibited 5.04 ± 1.97%, 5.00 ± 1.26%, and 1.80 ± 2.33% inhibitions, respectively at the concentration of 40 μM.

Although a variety of studies have been performed to determine biological activities of *C. ternata*, this is the only second report on ALR2 inhibition activity of this plant. While rat lens aldose reductase was used in an earlier report,[21] recombinant human aldose reductase was employed in this study. Furthermore, the aldose reductase inhibitory activities of isocorybulbine, corybulbine, and *N*-methyltetrahydroberbinium, to the best of our knowledge, were evaluated for the first time in this study. Whereas dehydrocorydaline showed moderate inhibitory activity in the previous report,[21] it did not exhibit any activity in this study possibly because recombinant human aldose reductase was used in this study. Other than dehydrocorydaline, corydaline and tetrahydropalmatine also showed stronger inhibitory activities in the previous report than in this study.[21]

The present study was carried out to search for new potential ALR2 inhibitors derived from *C. ternata*. Consequently, tetrahydrocoptisine (**1**), corybulbine (**5**), and *N*-methyltetrahydroberbinium (**7**) were found to show weak activities, even though their activities were not comparable to that of the extract. The reason why the activities of the isolated compounds from the active fractions were not comparable to the extract/fraction is considered that not single compounds but the combinations of each compounds contributed to the activity of the extract. Although there is a report on the aldose reductase inhibitory activities of Corydalis tuber, the present investigation was the first to use the recombinant human aldose reductase for the evaluation. In addition, to the best of our knowledge, the ALR2 inhibition activities of isocorybulbine, corybulbine, and *N*-methyltetrahydro-

berbinium were reported in this study for the first time.

In conclusion, the results in this study suggest a use of the extract of *C. ternata* for ameliorating diabetic complications.

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