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NOTE

Structure of diarylheptanoids with antiallergic activity from the rhizomes of *Curcuma comosa*

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Abstract The methanolic extract from the dried rhizomes of *Curcuma comosa* cultivated in Thailand was found to inhibit the release of β-hexosaminidase as a maker of degranulation from rat basophil leukemia (RBL-2H3) cells. Two new diarylheptanoids, diarylcomosols IV and V, were isolated from the methanolic extract. The chemical structures of the new compounds were elucidated on the basis of chemical and physicochemical evidence. The isolated diarylheptanoids showed inhibitory activity, and the structural requirements of the active constituents for the inhibition were clarified.

Keywords *Curcuma comosa* · Diarylheptanoids · Antiallergic activity · Thai traditional medicine

Introduction

A Zingiberaceae plant, *Curcuma comosa*, is widely distributed in tropical and subtropical regions of Asia, especially Thailand, Indonesia, and Malaysia. The rhizome of *C. comosa* has been used as an aromatic stomachic and anti-inflammatory [1, 2]. In the course of our studies on bioactive constituents from Thai traditional medicine [3–7], we previously reported the isolation from the rhizomes of *C. comosa* and the structure elucidation of diarylcomosols I (**16**), II (**11**), and III (**3**), and known compounds (3*R*′,5*S*′)-3,5-dihydroxy-1-(4′-hydroxy-3′,5′-dimethoxyphenyl)-7-(4″-hydroxy-3′-methoxyphenyl)heptane (**4**, 0.0067 %) [8], (3*R*′,5*S*′)-3,5-dihydroxy-1-(3′,4′-dihydroxyphenyl)-7-(4″-hydroxyphenyl)heptane (**5**, 0.0064 %) [9], (+)-hannokinol (**6**, 0.011 %) [10], (3*R*,5*R*)-3,5-diacetoxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptane (**7**, 0.0039 %) [9], (3*R*,5*R*)-3-acetoxy-5-hydroxy-1-(4-hydroxyphenyl)-7-(3,4-dihydroxyphenyl)heptane (**8**, 0.049 %) [9], (3*R*,5*R*)-3-acetoxy-5-hydroxy-1,7-bis(3,4-dihydroxyphenyl)heptane (**9**, 0.0027 %) [9], (3*R*,5*R*)-dihydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptane (**10**, 0.0044 %) [9], (3*R*)-1,7-bis(4-hydroxyphenyl)-(6*E*)-6-hepten-3-ol (**12**, 0.0042 %) [11], (*E*)-1,7-bis(4-hydroxyphenyl)-6-hepten-3-one (**13**, 0.0033 %) [11], platyphyllone (**14**, 0.0088 %) [12], (5*R*)-5-hydroxy-1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-3-heptanone (**15**, 0.0039 %) [13], and 1,7-bis(4-hydroxyphenyl)hepta-4*E*,6*E*-dien-3-one (**17**, 0.016 %) [14] with inhibitory effects on melanogenesis [15]. As a continuing study, we found that the methanolic (MeOH) extract from the dried rhizomes of *C.comosa* showed inhibitory activities on the release of β-hexosaminidase as a maker of degranulation from rat basophil leukemia (RBL-2H3) cells. From the MeOH extract, we have isolated two new diarylheptanoids, diarylcomosols IV (**1**) and V (**2**). The inhibitory effects of the isolated compounds were also investigated. This paper deals with the structure elucidation of the new constituents (**1** and **2**) and the antiallergic activity of the isolated compounds (Fig. 1).

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Results and discussion

A MeOH extract of the thermally-dried rhizomes of *C. comosa* showed inhibitory activities on the release of β-

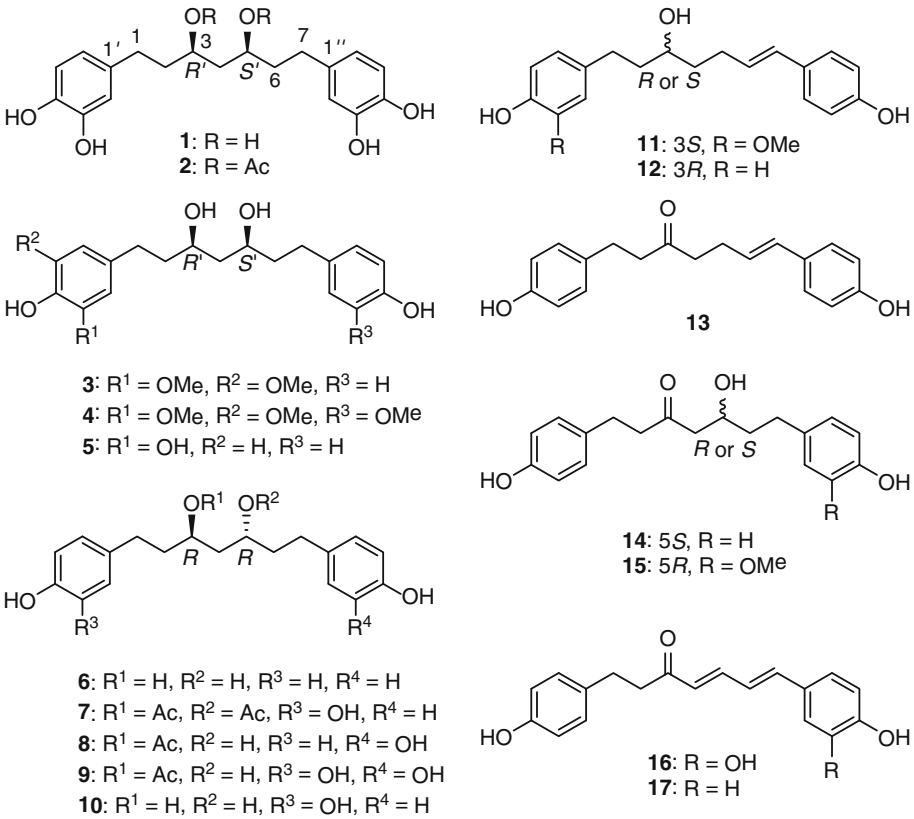

Fig. 1 Structure of constituents isolated from the rhizomes of *C. comosa*

hexosaminidase from RBL-2H3 cells [inhibition (%): 12.7 ± 3.2 ($p < 0.01$) at 100 μg/mL]. The MeOH extract was partitioned into an EtOAc–H_2O (1:1, v/v) mixture to furnish an EtOAc-soluble fraction (7.9 %) and an aqueous layer. The aqueous layer was further extracted with 1-butanol to give 1-butanol- (2.8 %) and H_2O- (15.3 %) soluble fractions. The EtOAc-soluble fractions were found to have significant inhibitory effects [inhibition (%): 28.2 ± 4.5 ($p < 0.01$) at 100 μg/mL]. The EtOAc-soluble fraction, a predominant bioactive portion, was subjected to normal- and reversed-phase silica-gel column chromatography and repeated HPLC to give two new diarylheptanoids, diarylcomosols IV (**1**, 0.0022 %) and V (**2**, 0.013 %).

Diarylcomosol IV (**1**) was isolated as pale yellow oil. The IR spectrum of **1** suggested the presence of hydroxy (3,590 cm^{-1}) and aromatic ring (1,606, 1,525 cm^{-1}). In the EIMS of **1**, a molecular ion peak $[M]^+$ was observed at *m/z* 348 and the molecular formula $C_{19}H_{24}O_6$ was determined by HRMS measurement of the molecular ion peak. The ^{1}H-NMR and ^{13}C-NMR (methanol-d_4) spectra of **1** (Table 1), which were assigned by various NMR experiments, showed signals assignable to five methylenes [δ 2.47 (2H, m, H-1a,7a), 2.55 (2H, m, H-1b,7b), 1.68 (4H, m, H_2-2,6), and 1.58 (2H, m, H_2-4)], two methines each bearing an oxygen function [δ 3.74 (2H, br-s, H-3, 5)], and

Table 1 ^{13}C-NMR (125 MHz) and ^{1}H-NMR (500 MHz) spectroscopic data for **1** and **2** measured in methanol-d_4

Position	**1**		**2**	
	δ C	δ H (J in Hz)	δ C	δ H (J in Hz)
1	32.1	2.47 (m)	31.9	2.44 (t, $J = 7.7$)
		2.55 (m)		
2	40.8	1.68 (m)	37.7	1.75 (m)
3	71.0	3.74 (br-s)	71.6	4.90 (m)
4	44.8	1.58 (m)	39.5	1.80 (t, $J = 6.9$)
5	71.0	3.74 (br-s)	71.6	4.90 (m)
6	40.8	1.68 (m)	37.7	1.75 (m)
7	32.1	2.47 (m)	31.9	2.44 (t, $J = 7.7$)
		2.55 (m)		
1′, 1″	135.3		134.3	
2′, 2″	116.5	6.61 (d, $J = 1.9$)	116.5	6.59 (d, $J = 1.9$)
3′, 3″	146.1		146.1	
4′, 4″	144.2		144.3	
5′, 5″	116.3	6.64 (d, $J = 7.9$)	116.3	6.65 (d, $J = 7.9$)
6′, 6″	120.6	6.48 (dd, $J = 1.9$, 7.9)	120.6	6.48 (dd, $J = 1.9$, 7.9)
3,5-OCOCH$_3$			172.7	
3,5-OCO*CH$_3$*			21.1	1.96 (s)

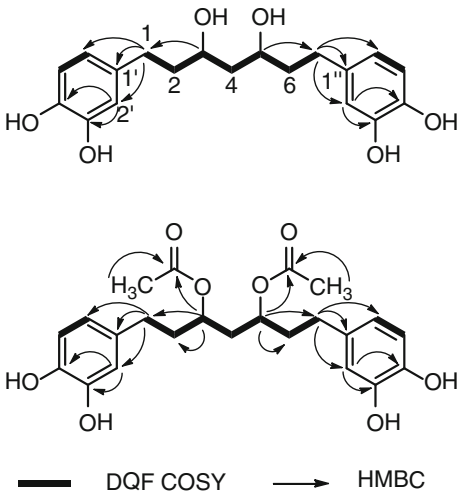

Fig. 2 Important 2D NMR correlations of **1** and **2**

two aromatic rings [δ 6.61 (2H, d, $J = 1.9$ Hz, H-2′,2″), 6.64 (2H, d, $J = 7.9$ Hz, H-5′,5″), 6.48 (2H, dd, $J = 1.9$, 7.9 Hz, H-6′,6″)]. From the DQF COSY and HMBC experiments (Fig. 2), the planar structure of **1** was determined to be the same as (3*R*,5*R*)-3,5-dihydroxy-1,7-bis(3,4-dihydroxyphenyl)heptane [16]. However, small differences in the ^{1}H- and ^{13}C-NMR spectrums were observed at the positions of C-2, 3, 4, 5, and 6. In addition, **1** was optically inactive, suggesting that the relative configuration at C-3 and C-5 was the syn type. On the basis of all this evidence, the chemical structure of diarylcomosol I (**1**) was determined to be (3*R*,5*S*)-3,5-dihydroxy-1,7-bis(3,4-dihydroxyphenyl)heptane.

Diarylcomosol V (**2**) was isolated as pale yellow oil. In the EIMS of **2**, a molecular ion peak $[M]^{+}$ was observed at *m/z* 432 and the molecular formula $C_{23}H_{28}O_8$ was determined by HRMS measurement of the molecular ion peak. The IR spectrum of **2** suggested the presence of hydroxy, aromatic ring, and ester. The ^{1}H-NMR and ^{13}C-NMR (methanol-d_4) spectra of **2** (Table 1) showed signals assignable to five methylenes, two methines each bearing an oxygen function, two aromatic rings, and two acetoxy groups [δ 1.96 (6H, s, 3,5-OCOCH_3)]. From the DQF COSY and HMBC experiments (Fig. 2), the planar structure of **2** was determined to be the same as (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(3,4-dihydroxyphenyl)heptane [17]. Next, small differences in the ^{1}H- and ^{13}C-NMR spectrums were observed at the positions of C-2, 3, 4, 5, 6, and acetoxy groups. In addition, **2** was optically inactive, suggesting that the relative configuration at C-3 and C-5 was the syn type. On the basis of all this evidence, the chemical structure of diarylcomosol V (**2**) was determined to be (3*R*,5*S*)-3,5-diacetoxy-1,7-bis(3,4-dihydroxyphenyl) heptane.

Table 2 Inhibitory effects of diarylheptanoids (**3**–**17**) from *C. comosa* on the release of β-hexosaminidase from RBL-2H3 cells

Sample	Inhibition (%)		
	10 μM	30 μM	100 μM
3	38.4 ± 2.5**	72.0 ± 2.3**	101.4 ± 0.5**
4	20.7 ± 2.7**	54.7 ± 2.0**	105.8 ± 1.1**
5	13.0 ± 2.0	25.5 ± 5.7**	80.7 ± 1.9**
6	19.0 ± 3.9	22.1 ± 6.9	86.5 ± 0.8**
7	19.7 ± 5.0**	53.0 ± 4.6**	94.6 ± 1.3**
8	9.5 ± 2.5	28.5 ± 4.1**	85.8 ± 0.5**
9	25.0 ± 8.0*	45.3 ± 3.6**	90.4 ± 1.2**
10	8.9 ± 4.0	9.9 ± 4.7	51.9 ± 4.8**
11	20.9 ± 2.2**	56.1 ± 3.0**	101.4 ± 1.1**
12	14.9 ± 8.4	34.4 ± 8.0**	101.5 ± 2.3**
13	−3.7 ± 5.0	24.8 ± 4.3**	116.5 ± 1.4**
14	47.3 ± 7.6**	66.7 ± 3.0**	110.1 ± 0.8**
15	35.1 ± 4.6**	62.6 ± 3.6**	104.0 ± 0.3**
16	14.3 ± 2.5**	32.3 ± 2.6**	66.6 ± 1.4**
17	−1.4 ± 2.9	33.8 ± 4.0**	113.2 ± 4.3**
Sample	Inhibition (%)		
	100 μM	150 μM	300 μM
Ketotifen	44.2 ± 1.6**	59.6 ± 3.2**	84.2 ± 1.9**

Each value represents the mean ± SEM ($n = 4$)

Significantly different from the control, *$p < 0.05$, **$p < 0.01$

In the course of our studies on antiallergic constituents from natural medicines [18–20], we previously reported that some triterpenes and oleanane-type triterpene oligoglycosides showed inhibitory effects on histamine release from rat exudate cells induced by an antigen–antibody reaction [21, 22] and on β-hexosaminidase release induced by dinitrophenylated bovine serum albumin (DNP-BSA) from RBL-2H3 cells sensitized with anti-DNP immunoglobulin E (IgE) [23–25]. As a continuation of this study, we examined the effects of diarylheptanoids on the release of β-hexosaminidase from RBL-2H3 cells. As shown in Table 2, all diarylheptanoids isolated from *C. comosa* displayed greater potency for inhibiting the release of β-hexosaminidase from RBL-2H3 cells [inhibition: > 51.9 % ($p < 0.01$) at 100 μM] than a reference compound, ketotifen [inhibition: 44.2 % ($p < 0.01$) at 100 μM]. Next, the structural requirements of the active sesquiterpenes were examined. Interestingly, compounds **3** [inhibition: 72.0 % ($p < 0.01$) at 30 μM] and **4** [inhibition: 54.7 % ($p < 0.01$) at 30 μM], with methoxy groups attached to the aromatic ring, showed stronger inhibitory effects than compound **5** [inhibition: 25.5 % ($p < 0.01$) at 30 μM], lacking a methoxy group. This result means that methylation of hydroxy groups attached to the aromatic

ring increases the inhibitory effects. Among the isolates, compounds **3** and **15** showed potent inhibitory effects [IC_{50} = 14.8, 18.7 μM, respectively].

Experimental

General

The following instruments were used to obtain physical data: specific rotations, Horiba SEPA-300 digital polarimeter (l = 5 cm); IR spectra, Thermo Electron Nexus 470; EIMS and HREIMS, JEOL JMS-GCMATE mass spectrometer; ^{1}H-NMR spectra, JEOL JNM-LA 500 (500 MHz) spectrometer; ^{13}C-NMR spectra, JEOL JNM-LA 500 (125 MHz) spectrometer; HPLC, Shimadzu SPD-10AVP UV–VIS detector. COSMOSIL 5C18-MS-II (250 × 4.6 mm i.d., 250 × 10 mm i.d. and 250 × 20 mm i.d.) columns were used for analytical and preparative purposes. The following materials were used for chromatography: normal-phase silica gel column chromatography, Silica gel BW-200 (Fuji Silysia Chemical, Ltd., 150–350 mesh); reversed-phase silica gel column chromatography, Chromatorex ODS DM1020T (Fuji Silysia Chemical, Ltd., 100–200 mesh); TLC, precoated TLC plates with Silica gel 60F_{254} (Merck, 0.25 mm) (ordinary phase) and Silica gel RP-18 F_{254S} (Merck, 0.25 mm) (reversed phase); reversed-phase HPTLC, precoated TLC plates with Silica gel RP-18 WF_{254S} (Merck, 0.25 mm). Detection was achieved by spraying with 1 % $Ce(SO_4)_2$–10 % aqueous H_2SO_4 followed by heating.

Plant material

The thermally-dried and sliced rhizomes of *C. comosa*, cultivated in Thailand, were purchased from Mae Chu Co. Ltd. (Nara, Japan) in 2012, and identified by one of the authors (M.Y.). A voucher specimen is on file in our laboratory (KPU CC-2012-1).

Extraction and isolation

The dried rhizomes (4.0 kg) were extracted three times with methanol under reflux for 3 h. Evaporation of the solvent under reduced pressure provided a MeOH extract (1,050 g, 26.3 %). A part of the MeOH extract (120 g) was partitioned into an EtOAc–H_2O (1:1, v/v) mixture to furnish an EtOAc-soluble fraction (36.0 g, 7.9 %) and an aqueous phase. The aqueous phase was further extracted with 1-butanol to give a 1-butanol-soluble fraction (13.0 g, 2.8 %) and a H_2O-soluble fraction (70.0 g, 15.3 %). The EtOAc-soluble fraction (36.0 g) was subjected to normal phase silica gel column chromatography [1.0 kg, *n*-hexane → *n*-hexane–$CHCl_3$ (5:1 → 2:1 → 1:2 v/v) → $CHCl_3$ → $CHCl_3$–MeOH (200:1 → 50:1 → 10:1 → 5:1 v/v) → MeOH] to give eight fractions [Fr.EA1, Fr.EA2, Fr.EA3, Fr.EA4, Fr.EA5, Fr.EA6 (5.1 g), Fr.EA7 (7.4 g), Fr.EA8]. Fraction EA6 (5.1 g) was further separated by reversed phase silica gel column chromatography [150.0 g, MeOH–H_2O (20:80 → 30:70 → 40:60 → 50:50 → 60:40, → 70:30, → 85:15 v/v) → MeOH] to give nine fractions [Fr.EA6-1, Fr.EA6-2, Fr.EA6-3, Fr.EA6-4 (341.4 mg), Fr.EA6-5, Fr.EA6-6 (392.0 mg), Fr.EA6-7, Fr.EA6-8, Fr.EA6-9 (568.2 mg)]. Fraction EA6-4 (341.4 mg) was purified by HPLC [H_2O–MeCN–AcOH (850: 150: 3, v/v/v)] to give **6** (50.3 mg). Fraction EA6-6 (392.0 mg) was purified by HPLC [H_2O–MeCN–AcOH (730:270:3, v/v/v)] to give **3** (53.1 mg), **4** (30.8 mg), **14** (40.1 mg), and **15** (17.8 mg). Fraction EA6-9 (568.2 mg) was purified by HPLC [H_2O–MeCN–AcOH (600:400:3, v/v/v)] to give **7** (17.8 mg), **11** (15.0 mg), **13** (15.1 mg), and **17** (72.0 mg). Fraction EA7 (7.4 g) was further separated by reversed phase silica gel column chromatography [150 g, MeOH–H2O (30:70 → 40:60 → 50:50 → 60:40, → 70:30, → 80:20 v/v) → MeOH] to give nine fractions [Fr.EA7-1, Fr.EA7-2 (0.98 g), Fr.EA7-3, Fr.EA7-4 (0.80 mg), Fr.EA7-5 (0.60 g), Fr.EA7-6, Fr.EA7-7, Fr.EA7-8, Fr.EA7-9]. Fraction EA7-2 (0.98 g) was subjected to normal phase silica gel column chromatography [30.0 g, *n*-hexane → *n*-hexane–$CHCl_3$ (1:1 → 1:2 v/v) → $CHCl_3$ → $CHCl_3$–MeOH (50:1 → 10:1 → 5:1 v/v) → MeOH] to give three fractions [Fr.EA7-2-1, Fr.EA7-2-2, Fr.EA7-2-3 (83.5 mg)]. Fraction EA7-2-3 (83.5 mg) was purified by HPLC [H_2O–MeCN–AcOH (800:200:3, v/v/v)] to give **5** (20.3 mg) and **10** (29.1 mg). Fraction EA7-4 (0.80 g) was purified by HPLC [H_2O–MeCN–AcOH (650:350:3, v/v/v)] to give **2** (58.0 mg), **8** (225.0 mg), and **9** (12.4 mg). Fraction EA7-5 (0.60 g) was purified by HPLC [H_2O–MeCN–AcOH (550:450:3, v/v/v)] to give **1** (10.1 mg), **12** (19.3 mg), and **16** (8.1 mg).

*Diarylcomosol IV (**1**)*

Pale yellow oil; IR (KBr): ν_{max} 3,590, 1,606, 1,525 cm^{-1}; ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) measured in methanol-d_4: given in Table 1; EIMS: *m/z* 348 $[M]^+$; HREIMS: *m/z* 348.1575 (calcd for $C_{19}H_{24}O_6$ $[M]^+$: *m/z* 348.1573).

*Diarylcomosol V (**2**)*

Pale yellow oil; IR (KBr): ν_{max} 3,610, 1,606, 1,528, 1,375 cm^{-1}; ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) measured in methanol-d_4: given in Table 1;

EIMS: *m/z* 432 $[M]^+$; HREIMS: *m/z* 432.1787 (calcd for $C_{23}H_{28}O_8$ $[M]^+$: *m/z* 432.1784).

Effects on the release of β-hexosaminidase from RBL-2H3 cells

The inhibitory effects of the test samples on the release of β-hexosaminidase from RBL-2H3 cells [Cell No. JCRB0023, obtained from Health Science Research Resources Bank (Osaka, Japan)] were evaluated by a method reported previously [23]. Briefly, RBL-2H3 cells were dispensed into 48-well plates at a concentration of 4×10^4 cells/well using Eagle's Minimum Essential Medium (MEM, Sigma) containing fetal calf serum (10 %), penicillin (100 units/ml), streptomycin (100 μg/ml), and 0.45 μg/ml of anti-DNP IgE, and these were incubated overnight at 37 °C in 5 % CO_2 for sensitization of the cells. The cells were then washed twice with 200 μl of Siraganian buffer [119 mmol/l NaCl, 5 mmol/l KCl, 0.4 mmol/l $MgCl_2$, 25 mmol/l piperazine-*N*,*N*′-bis(2-ethanesulfonic acid) (PIPES), and 40 mmol/l NaOH, pH 7.2], and incubated in 80 μl of Siraganian buffer [5.6 mmol/l glucose, 1 mmol/l $CaCl_2$, and 0.1 % bovine serum albmin (BSA) were added] for an additional 10 min at 37 °C. Aliquots (10 μl) of test sample solution were added to each well and incubated for 10 min, followed by the addition of 10 μl of antigen (DNP-BSA, final concentration 10 μg/ml) at 37 °C for 10 min to stimulate the cells to evoke allergic reactions (degranulation). The reaction was stopped by cooling in an ice bath for 10 min. The supernatant (40 μl) was transferred into a 96-well microplate and incubated with 40 μl of substrate (1 mmol/l *p*-nitrophenyl-*N*-acetyl-β-D-glucosaminide) in 0.1 mol/l citrate buffer (pH 4.5) at 37 °C for 2 h. The reaction was stopped by adding 200 μl of stop solution (0.1 mol/l Na_2CO_3/$NaHCO_3$, pH 10.0). The absorbance was measured using a microplate reader at 405 nm. The test sample was dissolved in dimethylsulfoxide (DMSO), and the solution was added to Siraganian buffer (final DMSO concentration 0.1 %).

The percent inhibition of the release of β-hexosaminidase by the test material was calculated using the following equation:

$$\text{Inhibition}\,(\%) = [1-(T-B-N)/(C-N)] \times 100.$$

Control (*C*): DNP-BSA (+), test sample (–); Test (*T*): DNP-BSA (+), test sample (+); Blank (*B*): DNP-BSA (–), test sample (+); Normal (*N*): DNP-BSA (–), test sample (–).

Under these conditions, it was calculated that 10–15 % of β-hexosaminidase was released from the cells in the control groups by determination of the total β-hexosaminidase activity after treatment with 0.05 % Triton X-100.

Statistics

Values were expressed as mean ± SEM. One-way analysis of variance following Dunnett's test was used for statistical analysis. Probability (*p*) values less than 0.05 were considered significant.

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