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Anti-Rheumatoid Arthritis Effect of the *Kochia scoparia* Fruits and Activity Comparison of Momordin Ic, its Prosapogenin and Sapogenin

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MeOH extract of *Kochia scoparia* was fractionated into $CHCl_3$-, EtOAc- and BuOH extracts and the last fraction were hydrolyzed by 3%-NaOH (MeOH-H_2O) to compare the bioactivities on antinociceptive and anti-inflammatory effects. Silica gel column chromatography of BuOH fraction afforded a large amount of 3-*O*-β-D-xylopyranosyl (1→3)-β-D-glucuronopyranosyl oleanolic acid (momordin Ic, **4**) and that of acid hydrolysate of BuOH fraction gave 3-*O*-β-D-glucuronopyranosyl oleanolic acid (momordin Ib, **3**), its 6′-*O*-methyl ester (**2**) and oleanolic acid (**1**). Silica gel column chromatography of alkaline hydrolysate afforded a large amount of **4**. MeOH extract and both EtOAc- and BuOH fractions were active in the rheumatoidal rat induced Freund's complete adjuvant reagent (FCA) whereas $CHCl_3$ fraction was inactive. Compound **1** and **4** showed significant activities in the same assay but oleanolic acid 3-*O*-glucuronopyranoside (**3**) showed no activity. These fashions were also observed in carrageenan-induced edema of the rat and in the antinociceptive activity tests undertaken in hot plate- and writhing methods. These results suggest that momordin Ic and its aglycone, oleanolic acid, could be active principles for rheumatoid arthritis.

Key words: *Kochia scoparia*, Chenopodiaceae, Momordin Ic, Oleanolic acid, Rheumatoid arthritis, Edema, Antinociceptive

INTRODUCTION

The fruits of *Kochia scoparia* (Chenopodiaceae) have been used for treatment of skin diseases in the Chinese medicine (Matsuda *et al.*, 1997a, b) and for remedy of diabetes mellitus and rheumatoidal arthritis in the folk medicine in Korea. It has been reported that this crude drug contains several of oleanolic acid glycosides (Wen *et al.*, 1995: Yoshikawa *et al.*, 1997). Momordin Ic is an active principle of antinociceptive, anti-inflammatory (Matsuda *et al.*, 1997a) and antiallergic activities (Matsuda *et al.*, 1997b). We have demonstrated that chemically transformed compounds of saponins could be active in anti-diabetic activity test *in vivo* (Kim *et al.*, 1998). The fractionation of MeOH extract, the preparation of hydrolyzed fraction from BuOH fraction and successive phytochemical isolations were undertaken. The samples obtained through a series of the procedures were assayed for the elucidation of active components on rheumatoid arthritis and for the structure-activity relationship.

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MATERIALS AND METHODS

Plant material, extraction and fractionation

The fruits of *Kochia scoparia* L. were purchased from the Chun-Il Oriental herbal store in Wonju, Korea and the plant origin was identified by S.Y. Yun (Division of Applied Plant Sciences, Sangji University, Korea. A voucher specimen (#NATCHEM-21) was deposited in Lab. of Natural Products Analysis, Division of Applied Plant Sciences, Sangji University. The plant material (2.5 kg) was extracted three times with MeOH under reflux. The extract was filtered and evaporated on a rotatory evaporator under reduced pressure. The concentrated

extract was again dried using freeze dryer to give a solid MeOH extract (243 g). The MeOH extract (200 g) was suspended with H_2O and partitioned with $CHCl_3$ followed by concentration of $CHCl_3$ fraction *in vacuo*. A viscous $CHCl_3$ fraction was dried in freeze dryer to give $CHCl_3$ extract (30 g). Water layer was successively partitioned with EtOAc and BuOH, and further the EtOAc- and BuOH-soluble fraction was dried on a rotatory evaporator *in vacuo* and dried in a freeze dryer to give masses of EtOAc (6 g) extract and BuOH (80 g) extract.

Isolation of momordin Ic

Fifteen g of BuOH extract was chromatographed over silica gel (320 g) using the eluent of $CHCl_3$-MeOH-H_2O (65:35:10, lower phase) and collected with 25 ml each. The fractions were checked by 50%-H_2SO_4 on TLC and the fractions showing on R_f 0.15 were taken. These were combined and concentrated followed by recrystallization from MeOH to give a white solid of momordin Ic.

Momordin Ic: amorphous white powder, mp 224-225°C(dec.), $[\alpha]_D^{26}$+47.9 (c=0.6, MeOH); IR ν_{max} (KBr) cm^{-1} : 3456 (OH), 2932, 2900, 1700, 1695 (COOH), 1150, 1070, 1030; ^{1}H-NMR (500 MHz, pyridine-d_5); 5.44 (1H, t-like, H-12), 3.32 (H-3), 5.31 (1H, d, J=7.2 Hz, H-1″ of xyl), 4.95 (1H, d, J=7.6 Hz, H-1′ of β-glcU), 1.30, 1.27, 0.99, 0.96, 0.94, 0.78, 0.76 (3H, each s, Me); ^{13}C-NMR (125 MHz, pyridine-d_5) δ; see literature (Kawamura *et al.*, 1983); FAB-MS (positive) *m/z*: 787 $[M+Na]^+$, 655 [M+Na-xyl]$^+$, 439 [oleanolic acid+H]$^+$.

Acid hydrolysis of BuOH fraction and isolation of oleanolic acid

A BuOH fraction (18 g), so called a saponin fraction, was hydrolyzed in 5%-HCl for 5h under reflux. After cooling, this was extracted with *n*-hexane and the extract was discarded. The residual water layer was extracted with EtOAc and the extract was washed with a small volume of H_2O and dehydrated with anhydrous sodium sulfate and followed by concentrating *in vacuo*. The resultant extract (2 g) was chromatographed over silica gel eluting with $CHCl_3$-MeOH-H_2O and collected by 40 ml each. The fractions showing on R_f 0.68, 0.53, and 0.21 were combined, respectively, and concentrated *in vacuo*. These were recrystallyzed in MeOH to give amorphous white solid. These were identified as oleanolic acid, 3-*O*-β-D-giucuronopyranosyl oleanolic acid (**3**, momordin Ib) and its 6′-*O*-methyl ester (**2**) by comparisons of mp, $[\alpha]_D$, IR, ^{1}H-NMR- and ^{13}C-NMR data.

Oleanolic acid: white powder, mp 196-198°C, $[\alpha]_D$ +64.6° (*c*=0.27, $CHCl_3$), ^{1}H-NMR (500 MHz, pyridine-d_5): 0.90 (3H, s, H-25), 0.95 (3H, s, H-29), 1.01 (2 × 3H, s, H-24, 30), 1.02 (3H, s, H-26), 1.23 (3H, s, H-23), 1.28 (3H, s, H-27), 3.28 (1H, dd-like, H-28), 3.43 (1H, dd-like, H-3), 5.48 (1H, br. s., H-12) ; MS *m/z* (%): 456 (M^+, 6), 248 (100), 207 (30), 204 (32), 203 (72), 189 (30); ^{13}C-NMR: see literatures (Yoshikawa *et al.*, 1997; Shao *et al.*, 1989).

Momordin Ib: mp 264-267°C, $[\alpha]_D$9 +20.4° (*c*=0.80, MeOH), IR 3400, 1720 (broad), 1100-100 cm^{-1}; ^{1}H-NMR (pyridine-d_5, 100 MHz) δ: 0.81 (3H, s, CH_3), 0.98 (3H, s, 4 × CH_3), 1.32 (3H, s, 2 × CH_3), 5.03 (1H, d, *J*=6.8 Hz, H-1 of GlcU), 5.46 (br. s., H-12); ^{13}C-NMR: see literatures (Yoshikawa *et al.*, 1997; Shao *et al.*, 1989).

Momordin Ib 6′-*O*-methyl ester: mp 201-202°C, IR ν_{max} (KBr) cm^{-1}: 3427 (OH), 2949 (CH), 1736 ($COOCH_3$), 1703 (COOH), 1463, 1389, 1165, 1059; ^{1}H-NMR (500 MHz, pyridine-d_5): 0.81 (3H, s, H-25), 0.95 (3H, s, H-29, 24), 0.98 (3H, s, H-26), 1.01 (3H, s, H-30), 1.29 (3H, s, H-23), 1.30 (3H, s, H-27), 3.28 (1H, dd-like, H-18), 3.36 (1H, dd, *J*=11.7 and 4.3 Hz), 4.05 (1H, dd, *J*=8.8 and 7.8 Hz, H-2′), 4.22 (1H, dd, *J*=9.0 and 8.8 Hz, H-3′), 4.43 (1H, dd, *J*=9.7 and 9.0 Hz, H-4′), 4.55 (1H, d, *J*=9.7 Hz, H-5′), 4.96 (1H, d, *J*=7.8 Hz, H-1′), 5.45 (1H, br. s, H-12); 13C-NMR (125 MHz, pyridine-d_5) δ; 15.5 (C-25), 17.0 (C-24), 17.4 (C-26), 18.5 (C-6), 23.7 (C-11), 23.7 (C-16), 23.8 (C-30), 26.2 (C-27), 26.6 (C-2), 28.2 (C-23), 28.4 (C-15), 31.0 (C-20), 33.2 (C-7), 33.2 (C-22), 33.3 (C-29), 34.3 (C-21), 37.0 (C-10), 38.7 (C-1), 39.5 (C-4), 39.8 (C-8), 42.0 (C-18), 42.2 (C-14), 46.5 (C-19), 46.7 (C-17), 48.1 (C-9), 52.0 (-OMe), 55.9 (C-5), 73.2 (C-4′), 75.4 (C-2′), 77.2 (C-5′), 77.9 (C-3′), 89.2 (C-3), 107.2 (C-1′), 122.5 (C-12), 144.9 (C-13), 170.8 (C-6′), 180.1 (C-28).

Alkaline hydrolysis of BuOH fraction and isolation of prosapogenins (2, 3 and 4)

BuOH fraction was hydrolyzed by 3%-NaOH solution in H_2O-MeOH (8:2) under reflux for 50 min. After cooling, this reaction mixture was acidified with *d*-HCl and extracted with EtOAc. This extract was washed with H_2O and dehydrated with anhydrous sodium sulfate followed by drying *in vacuo*. The resultant reaction mixture was chromatographed over silica gel with $CHCl_3$-MeOH-H_2O (7:3:1, lower phase) to give momordin Ic which was identified by direct comparisons of TLC, mp, $[\alpha]_D$ and NMR data with authentic specimen.

Animals

Both 4 week-old ICR male mice and Sprague-Dawley male rats were purchased from Korean Experimental Animal Co. and adapted them in a constant condition (temperature: 20 ± 2°C, dampness: 40-60%, light/dark

cycle: 12 hr) for two weeks or more. Twenty-four hours before the experiment, only water was offered to the animals. Considering the variation of enzyme activity during one day, the animals were sacrificed at fixed time (10:00 A.M.-12:00 A.M.).

Induction of rheumatoid arthritis

Each 0.05 ml of Freund's complete adjuvant reagent (FCA reagent; Difco, USA) was injected to right hind paw of rats. Two weeks later, the induction of rheumatoid arthritis in rats was confirmed. The test samples, MeOH extract, $CHCl_3$-, EtOAc- and *n*-BuOH fractions were dissolved in DMSO and those solutions with various concentrations were made by dilution with saline. The samples of isolates (**1**, **3** and **4**) were also prepared like the extract samples. After the final treatment of the samples, the animals were anesthetized and the blood was taken from abdomen aorta. The constant volumes of the blood were preserved in CBC bottles and the remnants were coagulated at room temperature by standing for 30 min. This serum was collected for use by centrifuging (600 × g, 15 min).

Rheumatoidal arthritis was confirmed 2 weeks after the injection of FCA reagent to the right hind paw of rats. The test solutions (each, 150 and 200 mg/kg, p.o.) of extracts and those of isolates (5 and 10 mg/kg, I,p.) had been orally administered for 3, 5, 7 and 10 days. The effect was taken by plethysmometer (Ugo Basile, Italy). Methotrexate (MTX), an anti-rheumatoid arthritis drug, was used for the positive control. The inhibitory effect was calculated as follows: Inhibitory effect of edema (%)=(volume of control group-volume of treatment group/volume of control group) × 100

Induction of edema by carrageenan: Each 0.1 ml of 1% carrageenan (Sigma Co., U.S.A.) was injected to right footprints of rats and edema was induced. The test solution (each extract: 150, 250 mg/kg, p.o.; each compound: 5, 10 mg/kg, i.p.) had been administered for 7 days prior to the injection of carrageenan. Indomethacin, an anti-inflammatory drug, was used for the positive control. The effect was taken by plethysmometer (Ugo Basile, Italy) (Winter *et al.*, 1962). The inhibitory effect was calculated as follows: Inhibitory effect of edema (%)=(volume of control group-volume of treatment group/volume of control group) × 100

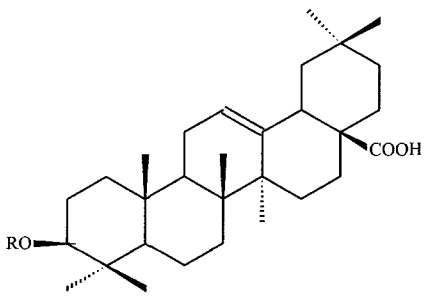
Acetic acid-induced writhing and hot plate method

Test solution was orally or intraperitoneally administered 30 min before the experiment, and further 0.1 ml/10 g of 0.7% acetic acid-saline was injected intraperitoneally. Ten min after the injection, the frequency of writhing in mice was counted for 10 min (Whittle, 1949). Aminopyrine (100 mg/kg) was used as a positive control agent. Hot plate made by Ugo Basile (Italy) was used for the measurement of antinociceptive effect by hot plate method. The response-time showing writhing syndrome was recorded.

RESULTS AND DISCUSSION

Solvent fractionation of the MeOH extract gave $CHCl_3$-, EtOAc- and BuOH fractions. Phytochemical isolation of BuOH fraction yielded a large amount of momordin Ic [3-*O*-β-D-xylopyranosyl (1→3)-β-D-glucuronopyranosyl oleanolic acid, **4**]. Isolation of acid-hydrolyzed fraction afforded oleanolic acid (**1**), 3-*O*-β-D-glucuronopyranosyl oleanolic acid (momordin Ib, **3**) and its 6′-*O*-methylester (**2**). Silica gel column chromatography of a partially-hydrolyzed fraction from BuOH extract yielded also momordin Ic. The structures were shown in Fig. 1. Momordins have been isolated from *Momordica cochinchinensis* (Kawamura *et al.*, 1988). A completely hydrolyzed compound, oleanolic acid, was observed in the extract by thin layer chromatography but its monosaccharides (2, 3) were not found. Momordin Ib 6′-*O*-methyl ester could be produced from the partial hydrolysis of 6′-*O*-methyl ester of momordin Ic whereas momordin Ib from momordin Ic. The assignment of momordin Ib 6′-*O*-methyl ester is firstly reported by the interpretation of ^{1}H-^{1}H COSY-, ^{1}H-^{13}C COSY-, DEPT NMR spectra as described in experimental section.

The extracts were orally administered for the real effect of *K. scoparia* (Table I-III) whereas the isolates were intraperitoneally administered for only activity comparisons (Fig. 2-5). The inhibitory effects on the edema induced by FCA were shown in Table 1 and Fig. 2. Table 1 implies the extracts containing momordin Ic, e.g., EtOAc- and BuOH- extract and hydrolysate of BuOH extract, inhibit edema. The groups treated with 5 mg/kg



1: R=H (oleanolic acid)
2: R=3-*O*-[6′-O-methyl β-D-glucuronopyranosyl] (momordin Ib 6′-*O*-methyl ester)
3: R=3-*O*-β-D-glucuronopyranosyl (momordin Ib)
4: R=3-*O*-[β-D-xylopyranosyl (1→3)-β-D-glucuronopyranosyl] (momordin Ic)

Fig. 1. Structures of oleanolic acid derivatives obtained from the fruits of *Kochia scoparia*

Table . Day and dose response of Kochia scoparia on anti-inflammatory effect in rats induced by FCA reagent.

Group	Dose (mg/kg)	Swelling (%)				
		0	3	5	7	10 (days)
Control	-	74.6 ± 3.52	78.4 ± 5.17**	79.9 ± 3.10	82.6 ± 3.47	84.3 ± 3.49
MeOH ext.	100		76.4 ± 3.27	73.4 ± 3.19	73.2 ± 4.27	74.6 ± 4.17
	250		77.0 ± 2.96	70.4 ± 2.47*	68.9 ± 3.56*	66.8 ± 4.53*
$CHCl_3$ ext.	100		73.5 ± 3.77	78.4 ± 3.99	81.4 ± 4.10	84.6 ± 4.97
	250		72.8 ± 2.89	80.3 ± 3.74	83.9 ± 2.47	79.4 ± 3.82
EtOAc ext.	100		73.9 ± 4.27	72.4 ± 2.97*	72.6 ± 3.22	73.6 ± 5.23
	250		72.8 ± 2.89	70.8 ± 2.46*	65.3 ± 3.06*	62.8 ± 3.27**
BuOH ext.	100		75.8 ± 3.86	71.6 ± 3.30*	62.7 ± 2.59*	70.3 ± 3.96*
	250		74.9 ± 4.84	69.3 ± 2.58*	53.2 ± 3.17**	65.4 ± 4.10*
Hydrolysate	100		76.3 ± 3.97	69.5 ± 2.96*	60.2 ± 3.27*	67.3 ± 3.17*
of BuOH ext.	250		74.9 ± 4.84	69.3 ± 2.58*	51.4 ± 2.40**	61.4 ± 3.64*
MTX	10 (i.p.)		68.2 ± 4.13	53.8 ± 2.86**	40.6 ± 2.17***	37.7 ± 3.19***

Values represent means ± S.E.M. (n=10). ***p<0.001, **p<0.01, *p<0.05 compared with the control.

Table II. Antiinflammatory effect of Kochia scoparia on carrageenan-induced edema of the hind paw in rats

Group	Dose (mg/kg)	Swelling (%)			
		30 min	60 min	90 min	120 min
Control	-	19.2 ± 2.43	26.4 ± 3.11	31.8 ± 2.19	41.6 ± 4.17
MeOH ext.	100	21.6 ± 2.17	25.8 ± 2.14	25.8 ± 1.46*	38.2 ± 3.10
	250	20.9 ± 3.10	23.4 ± 1.98	20.9 ± 2.16	27.8 ± 2.47**
$CHCl_3$ ext.	100	20.6 ± 1.43	27.6 ± 2.15	30.6 ± 1.94	40.3 ± 3.27
	250	21.7 ± 2.62	26.9 ± 1.86	33.2 ± 2.33	38.7 ± 2.97
EtOAc ext.	100	19.1 ± 2.47	25.2 ± 2.11	26.3 ± 2.26*	28.9 ± 1.77*
	250	19.3 ± 2.30	24.7 ± 1.96	25.9 ± 3.10*	23.7 ± 2.43**
BuOH ext.	100	19.5 ± 2.10	21.9 ± 2.33*	21.3 ± 3.16*	35.7 ± 2.17*
	250	18,9 ± 1.89	20.3 ± 2.16*	18.6 ± 2.42**	25.8 ± 1.99**
Hydrolysate of	100	22.3 ± 2.10	20.4 ± 2.36*	20.7 ± 2.17*	28.4 ± 2.43**
BuOH ext.	250	19.4 ± 1.98	18.7 ± 2.14*	17.6 ± 1.52**	22.9 ± 2.10**
Indomethacin	100	17.3 ± 1.58	15.8 ± 1.34**	10.6 ± 1.23**	11.7 ± 1.59***

Values represent means ± S.E.M. (n=10). ***p<0.001, **p<0.01, *p<0.05 compared with the control.

Table III. Antinociceptive effect of the extracts of Kochia scoparia and the components by acetic acid-induced writhing and hot-plate method in mice.

Group	Dose (mg/kg)	Frequency (Count/10 min)	Action time (sec)
Control	None	45.0 ± 2.63	28.4 ± 3.2
MeOH ext.	100 (p.o.)	35.7 ± 3.51	43.7 ± 2.5*
	250 (p.o.)	34.1 ± 3.74*	48.1 ± 3.6*
	500 (p.o.)	30.0 ± 2.7*	50.3 ± 3.1*
$CHCl_3$ ext.	100 (p.o.)	42.6 ± 4.50	32.7 ± 3.16
	250 (p.o.)	43.7 ± 5.51	33.6 ± 4.14
	500 (p.o.)	40.6 ± 3.52	35.4 ± 4.40
EtOAc ext.	100 (p.o.)	40.7 ± 4.5	38.2 ± 3.6
	250 (p.o.)	39.7 ± 5.5	43.9 ± 4.7
	500 (p.o.)	36.7 ±3.5	45.2 ± 5.2
BuOH ext.	100 (p.o.)	30.0 ± 2.7*	47.3 ± 4.2*
	250 (p.o.)	28.3 ± 3.6*	54.2 ± 4.0*
	500 (p.o.)	26.9 ± 2.4**	53.6 ± 4.2**
BuOH hyd.	100 (p.o.)	29.7 ± 3.5*	50.6 ± 3.5*
	250 (p.o.)	25.2 ± 2.1**	58.2 ± 5.2**
	500 (p.o.)	19.7 ± 3.5***	63.7 ± 2.4**

Values represent means±S.E.M. (n=10). ***p<0.001, **p<0.01, *p<0.05. Values in the parentheses are % antinociceptive effect to control group.

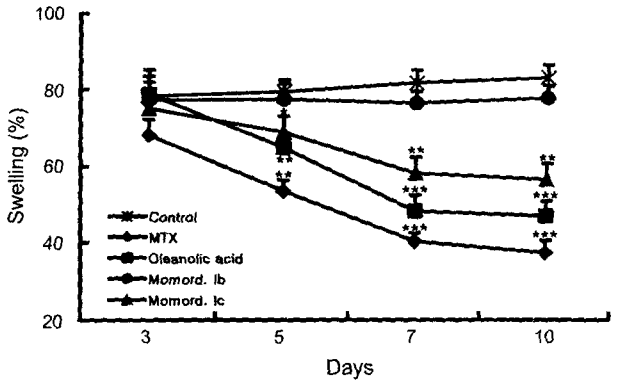


Fig. 2. Effect of the compounds (each 10 mg/kg, i.p.) obtained from *Kochia scoparia* on edema induced by FCA in the rat. {Values represent mean ± S.E. (n=10); *P<0.05, **P<0.01 and ***P<0.001, compared with the control, as analyzed with the Student t-test.}

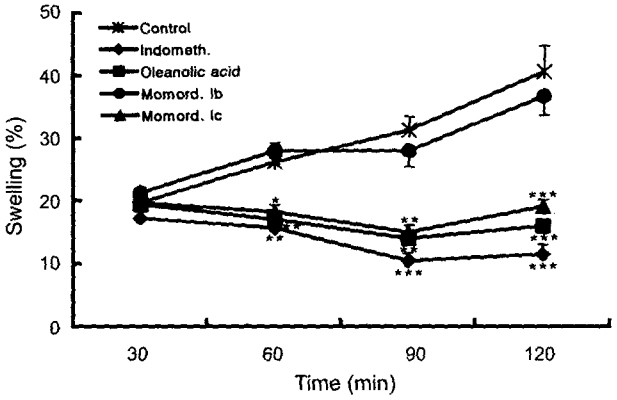


Fig. 3. Effect of the compounds {each 10 mg/kg, (i.p.); indometh. 100 mg/kg (p.o.)} obtained from *Kochia scoparia* on edema induced by carrageenan in the rat. {Values represent mean ± S.E. (n=10); *P<0.05, **P<0.01 and ***P<0.001, compared with the control, as analyzed with the Students t-test.}

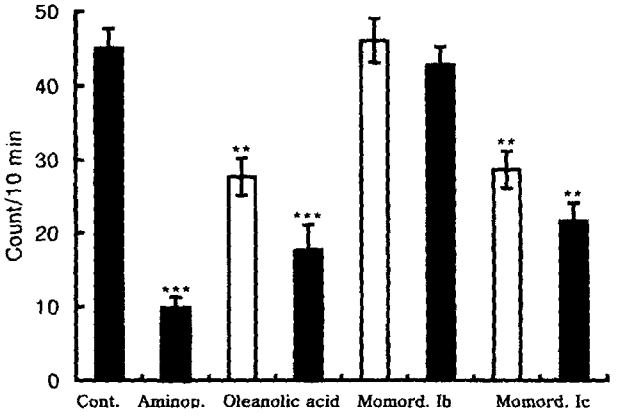


Fig. 4. Effect of the compounds isolated from *K. scoparia* on the action time induced by acetic acid in mice. Values represent means ± S.E. (n=10); *P<0.05, **P<0.01 and ***P<0.001, compared with the control, as analyzed with the Student t-test. white bars (5 mg/kg, i.p.) and black bars (10 mg/kg, i.p.) except for aminopyrine (100 mg/kg, p.o.).

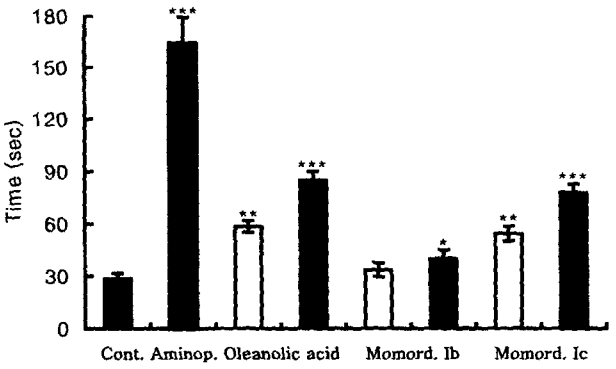


Fig. 5. Effect of the compounds isolated from *K. scoparia* on the action time induced by hot plate in mice. Values represent means ± S.E. (n=10); *P<0.05, **P<0.01 and ***P<0.001, compared with the control,as analyzed with the Students t-test.; white bars (5 mg/kg, i.p.) and black bars (10 mg/kg, i.p.) except for aminopyrine (100 mg/kg, p.o.).

(i.p.) exhibited a slightly weaker activity than with 10 mg/kg (data not shown). This result shows the effects of a hydrolyzed fraction are slightly more potent than the corresponding fraction not hydrolyzed. However, the activity difference was not significant and this could suggest that monodesmosides are predominantly contained in the *Kochia scoparia* fruit. Momordin Ic and its aglycone, oleanolic acid, showed significant anti-edema effects in the rat induced by FCA reagent whereas 3-*O*-β-D-glucuronopyranosyl oleanolic acid (**3**) exhibited no activity. It has been suggested that a number of glycosides including saponins could be hydrolyzed in the gastrointestinal tract (Kim *et al.*, 1998). Therefore, we suggest that an aglycone, oleanolic acid, could be also an active principle in addition to momordin Ic. Giner-Larza *et al.* (2001) have reported that oleanolic acid and its oxidized compound, oleanonic acid, have anti-inflammatory activity in mice induced by 12-deoxyphorbol-13-phenyl acetate, bradykinin and phospholipase. It has been reported that hepatoprotective action of oleanolic acid-enriched extract of *Ligustrum lucidum* fruits is mediated through an enhancement on hepatic glutathione regeneration capacity in mice (Yim *et al.*, 2001).

Although Matsuda *et al.* (1997) have reported the antiinflammatory effect of momordin Ic in the rat induced by carrageenan, we also assayed this activity by the nearly same method to discuss structure-activity relationship. This result shown in Table II was nearly the same as that in FCA-induced anti-edema test. Momordin Ib (3) was inactive but other two compounds, momordin Ic and oleanolic acid, were active. Of the products possibly producible in the intestine from momordin Ic, the triterpene momosaccharide is not active in this assay system. From these results, it was suggested that active triterpene derivatives in FCA-induced assay could be also

active in the other carrageenan-induced one. In general, treatment of FCA induces edema two weeks later but that of carrageenan 60 min later indicating the former edema is chronic and the latter is acute. The two assays may share the same process of vascular permeability that could be caused by kinins as observed in the reported mechanism of kalopanaxsaponin A on rheumatoid arthritis (Choi *et al.*, 2001a, b). These properties were also observed in the antinociceptive activity by hot plate method and acetic acid-induced writhing method. Significant effects were observed in the groups treated with MeOH extract, EtOAc extract, BuOH extract and alkaline hydrolysate of BuOH extract (Table III). Momordin Ic and oleanolic acid had significant antinociceptive effects as shown in Fig. 4 and 5. Since structure-activity relationship on edema and pain were found as similar fashions it was assumed that the same mediator could be involved in those inductions.

It has been reported that oleanolic acid glycosides inhibit gastric emptying in mice in 1.5% CMC-Na test meal loaded mice (Matsuda *et al.*, 1999a). Matsuda *et al.* have reported that momordin Ic (10 mg/kg, p.o.) potentially inhibited ethanol-induced gastric mucosal lesions with the suggestion on the roles of capsaicin-sensitive sensory nerves (Matsuda *et al.*, 1999b). Taken together with these reports and our data, it was suggested that the fruits of *Kochia scoparia* have merits for the remedy of rheumatoid arthritis. The antirheumatoid arthritis effect on *Kochia scoparia* has not been reported before.

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