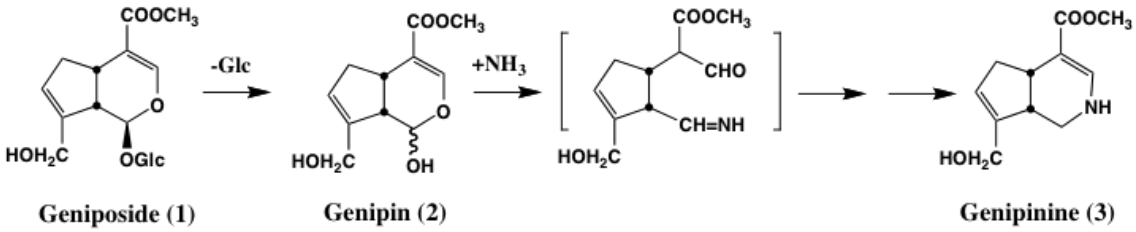
Geniposide



Geniposide (1) Genipin (2) Genipinine (3)

Metabolic process of geniposide by a human intestinal flora and *Klebsiella pneumoniae*

代謝実験

腸内細菌代謝　ヒト腸内細菌フローラ、ヒト腸内細菌 *Klebsiella pneumoniae*

Genipinine

$[\alpha]_D$: + 256° (*c* 0.04, MeOH). HRMS: Observed, *m/z* 209.1053, Calcd for $C_{11}H_{15}NO_3$: *m/z* 209.1052 (M^+). EI-MS *m/z*: 209 (100, M^+), 191 (19, M^+ - H_2O), 178 (- COOMe), 138 (26), 132 (26). ^{1}H-NMR (270 MHz, $CDCl_3$), δ 2.00 (1H, m, 6-Ha), 2.58 (1H, m, 9-H), 2.71 (1H, t, *J*= 11.0 Hz, 1-Ha), 2.88 (1H, m, 6-Hb), 3.14 (1H, ddd, *J*= 16.1, 8.1, 9.2 Hz, 5-H), 3.41 (1H, ddd, *J*= 11.0, 4.2, 5.9Hz, 1-Hb), 3.69 (3H, s, 4-COOMe), 4.24 (2H, s, 8-CH_2OH), 4.58 (1H, br. s, 2-H), 5.75 (1H, br. s, 7-H), 7.58 (lH, d, *J*=5.9Hz, 3-H). [Kawata *et al.*, *Planta Med*., **57**, 536-542 (1991)]

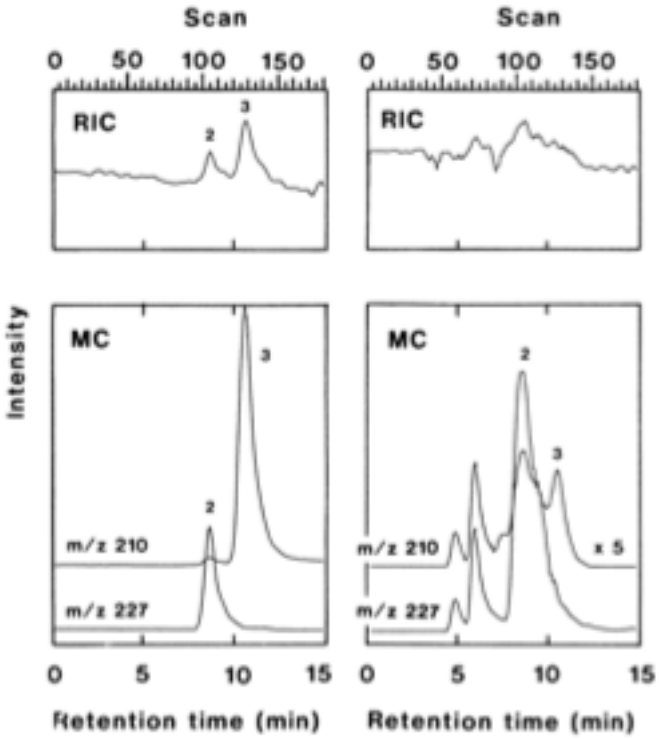


Fig. 1 Reconstructed ion current and mass chromatograms (RIC and MC) of the metabolites produced from geniposide (**1**) by *Klebsiella. pneumoniae* (right) and of authentic genipin (**2**) and genipinine (**3**) (left).

A Frit-FAB LC/MS system was used for analysis under the following conditions: column, μS Finepak C18 (1.5 mm i.d. x 250 mm); mobile phase, CH_3CN-H_2O-glycerol (20:80:0.3); flow rate, 0.1 ml/min; detection, FAB-MS in the positive ion mode. [Kawata *et al.*, *Planta Med*., **57**, 536-542 (1991)]

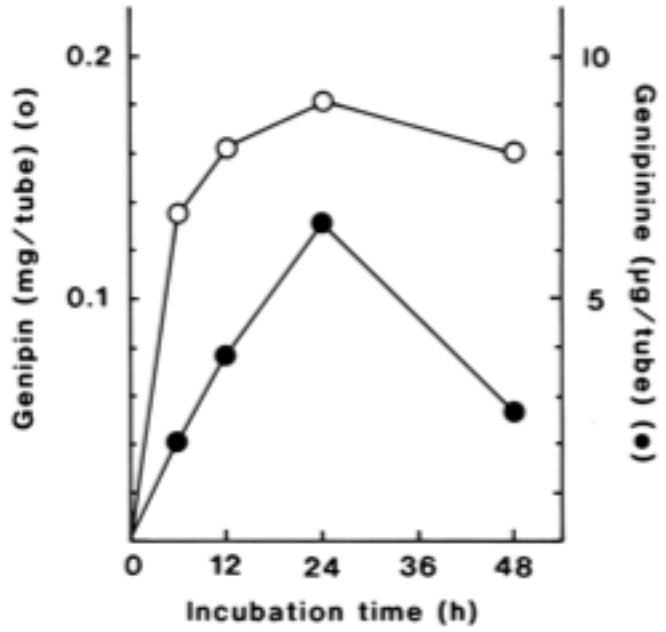


Fig. 2 Time course of the formation of genipin (**2**) and genipinine (**3**) from geniposide (**1**) by *K. pneumoniae*

(○), genipine; (●), genipinine

Tubes containing **1** (10 mg) and a suspension of *K. pneumoniae* in 100 mM phosphate buffer, pH 7.3, were anaerobically incubated for indicated periods at 37 °C, and the products extracted with EtOAc were quantitatively analyzed by LC/MS, monitoring the selected ions at *m/z* 210 (**3**) and 227 (**2**).

K. pneumoniae was anaerobically cultured in GAM broth (500 ml) for 24 h at 37 °C and the culture was centrifuged at 5700 x g for 5 min. The precipitates were suspended in 0.1 M phosphate buffer (pH 7.3; 50 ml) and the suspension was divided into tubes (5 ml/tube). Ten mg of **1** was added to each tube and the tubes were anaerobically incubated at intervals at 37 °C. The incubation mixture was extracted with EtOAc (5 ml x 2) and the combined EtOAc solutions were evaporated *in vacuo* to give a residue. The residue was dissolved in 100 μl of MeOH, and 4 μl of the solution were injected to a column of μS C18 and analyzed by LC/MS. The amounts of the primary aglycones and nitrogen-containing compounds were determined by means of selected ion monitoring (SIM), using calibration lines prepared with authentic samples. [Kawata *et al.*, *Planta*

Med., **57**, 536-542 (1991)]

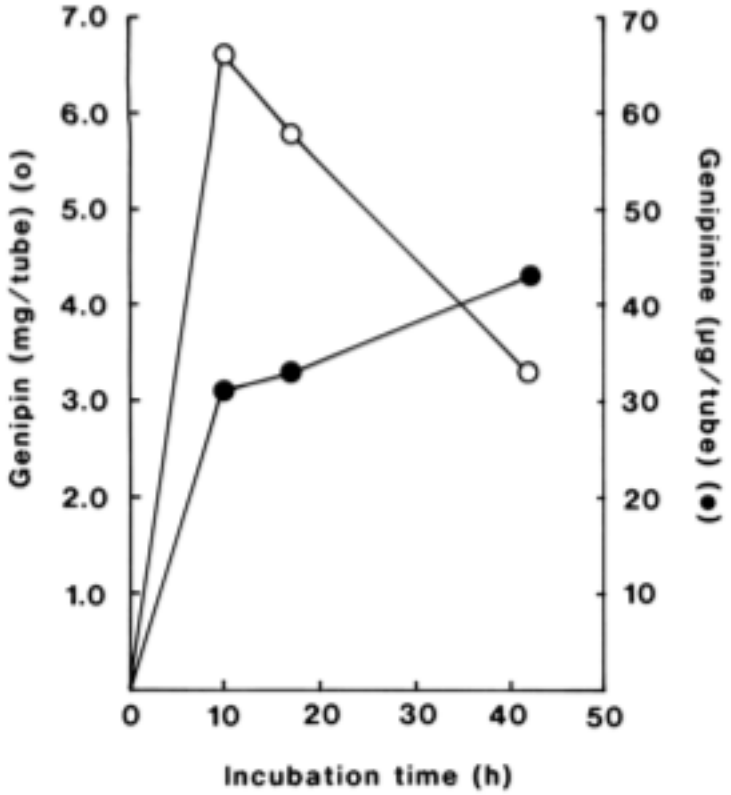


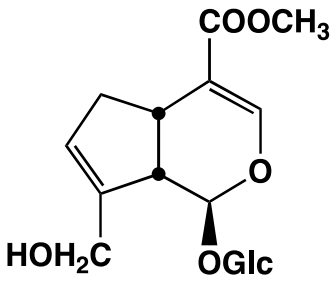
Fig. 3 Time course of the formation of genipin (**2**) and genipinine (**3**) from geniposide (**1**) by fecal flora
(○), genipine; (●), genipinine. Tubes containing **1** (30 mg) and a fecal suspension in 100 mM phosphate buffer, pH 7.3, were anaerobically incubated. The products were quantitatively analyzed by LC/MS.

Feces (10 g) obtained from a healthy man was suspended in 100 mM phosphate buffer (pH 7.3; 100ml). Tubes containing **1** (30 mg) and the suspension (10 ml) were anaerobi cally incubated for 10, 17, and 42 h at 37 °C. The mixture was then extracted with EtOAc (7 ml x 2) and the combined solutions were evaporated *in vacuo* to give a residue. The residue was dissolved in MeOH (60 μl) and a 1 μl aliquot was analyzed by LC/MS. [Kawata *et al.*, *Planta Med*., **57**, 536-542 (1991)]

参考文献

1)　Kawata Y., Hattori M., Akao T., Kobashi K. and Namba T.: Formation of nitrogen-containing metabolites from geniposide and gardenoside by human intestinal bacteria. *Planta Med*., **57**, 536-542 (1991).

Geniposide



Geniposide

【化合物】Geniposide

【測定機器】HPLC

【対象】ラットに茵蔯蒿湯（Yin Chen Hao Tang）を投与し、血清ンプルを分析。Sample1; 18g of 茵蔯蒿(YCH), Sample2; 18.0g of YCH+9.0g of 山梔子(ZZ), Sample3; 18.0g of YCH+6.0g of 大黄(DH), Sample4; 茵蔯蒿湯(YCHTP), Sample5; 9.0g of ZZ.

【代謝パラメータ】

Pharmacokinetic parameters of geniposide in rat plasma after oral administration of Yin Chen Hao Tang preparation

	Sample 2	Sample 4	Sample 5
C_{max} (μ g/ml)	13.66±1.71	11.54±2.73	8,81±1.31
T_{max} (h)	0.33±0.02	0.27±0.06	0.28±0.02
$t_{1/2}$ (h)	5.68±0.65	11.55±2.01	3.33±0.41
K_c (1/h)	0.12±0.02	0.06±0.01	0.26±0.03
$AUC_{0-\infty}$ (μ g/ml) x h	69.8±7.10	54.56±5.64	42.38±3.37
AUC_{0-t} (μ g/ml) x h	62.49±6.67	45.47±3.66	39.29±3.15

Mean±SD

【参考文献】

H. Lv, H. Sun, W. Sun, L. Liu, P. Wang, X. Wang, H. Cao, Pharmacokinetic studies of a Chinese triple herbal drug formula. *Phytomedicine* **15**, 993–1001 (2008).