DEFENCE FUNCTION OF GINSENOSIDES AGAINST SEVERAL METABOLIC DISORDERS IN THE ANIMAL BODY

Chung No Joo

Department of Biochemistry, College of Science
Yonsei University, Seoul 120-749

During the past two decades, physiological and biochemical approaches to elucidate the mechanism of ginsenosides effect on the body have been made intensively. However, it is still controversial whether appreciable amounts of ginsenosides could be absorbed orally to explain the results obtained from *in vivo* as well as *in vitro* experiments. Therefore, I will discuss first the metabolsim of orally administered ginsenosides, follwed by their defence function against several metabolic disorders in the animal body.

It has been demonstrated by several workers(Han *et. al.*, 1976 ; Odani *et. al.*, 1983 ; Lee and Joo, 1983) that orally administered ginsenosides are distributed in various tissues. However, it is uncertain whether ginsenosides are absorbed as such an unhydrolyzed form, or partially dissociated and/or metabolized forms.

We have synthesized ^{14}C-labelled ginsenosides from [U-^{14}C]-acetate using fresh raw ginseng root slices as an enz yme source and found that the synthesized ^{14}C-ginsenoside mixture showed an almost similar pattern as that of natural ginsenosides extracted from dried panax ginseng roots by HPLC but their relative amounts were different(Fig. 1). Table 1 showed the radioactivity distribution in the synthesized ^{14}C-

Table 1. Radioactivity distribution of ginsenosides synthesized from [U-^{14}C] acetate.

Total Radioactivity (cpm)	Radioactivity($\times 10^4$ cpm) (% recovered)							
BuOH extract	Ro	Ra	Rb_1	Rb_2, Rc	Rd, Re	Rf	Rg_1	Rg_2
1.49×10^8	730	25	209	546	690	571	863	396
(100)	(4.90)	(1.68)	(1.40)	(3.66)	(4.63)	(3.83)	(5.79)	(2.66)

Table 2. Radioactivity distribution in mouse tissues after the oral administration of 1mg of radioactive ginsenoside Rg_1(0.698μCi/mg/mouse). The mouse was anethetized with ethyl ether at 1, 3, 5, 12, and 24 hours after the rdioactive Rg_1 administration.

	Recovered Radioacitivity(cpm)						
Time(hr)	Liver	Brain	Small intestine	Large intestine	Blood	Urine	Feces
1	35,100	904	11,440	18,840	3,933	9,542	1,148
	(2.29)	(0.059)	(0.75)	(1.23)	(0.256)	(0.62)	(0.08)
3	84,180	820	171,050	79,140	3,238	29,839	7,835
	(5.489)	(0.053)	(11.14)	(5.15)	(0.211)	(1.94)	(0.52)
5	44,400	556	61,790	138,240	2,313	69,643	58,098
	(2.89)	(0.036)	(4.02)	(9.00)	(0.151)	(4.53)	(3.78)
12	34,440	512	17,600	12,910	513	102,543	79,298
	(2.05)	(0.033)	(1.15)	(0.84)	(0.033)	(6.68)	(5.16)
24	19,500	376	26,200	15,360	393	132,879	87,408
	(1.27)	(0.024)	(1.71)	(1.00)	(0.026)	(8.65)	(5.69)

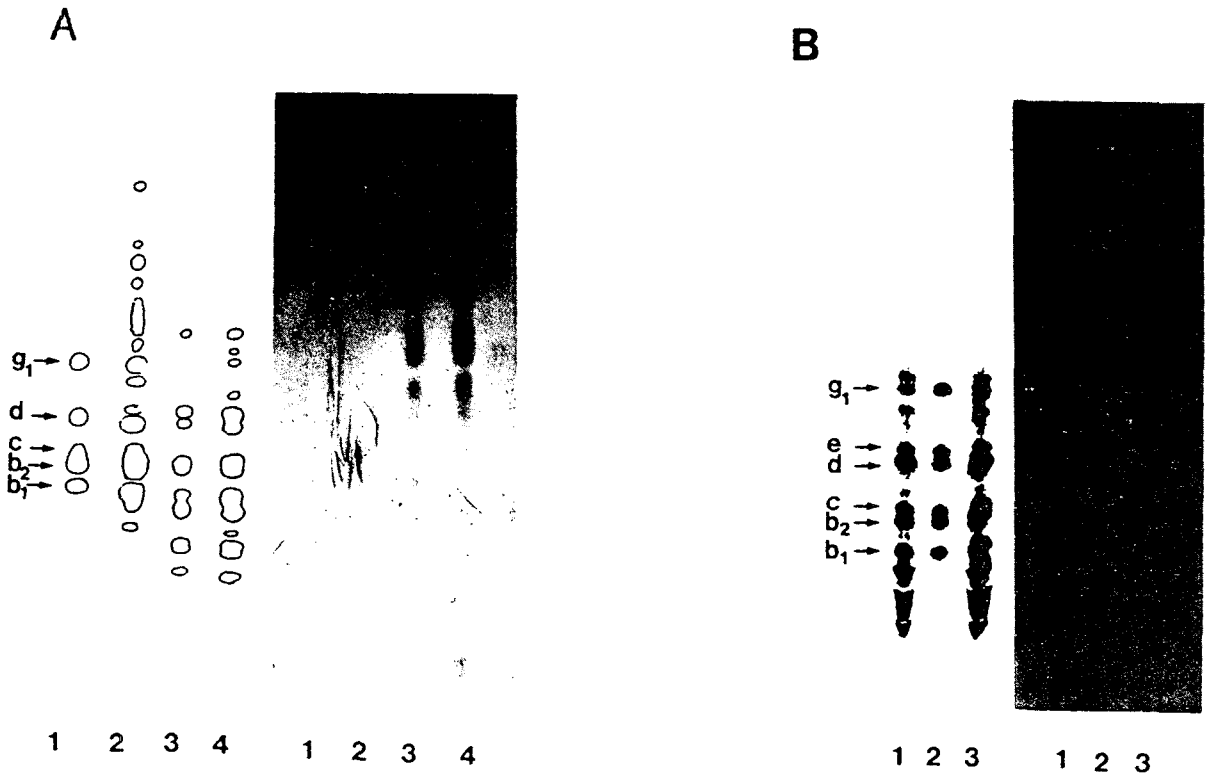

Fig. 1-a. Autoradiograms of ^{14}C-labelled ginsenosides synthesized from [U-^{14}C] acetate.
A. 1. standard ginsenosides Rb_1, Rb_2, Rc, Rd, Rg_1. 2. total ginsenosides extracted.
3. 4. synthesized ^{14}C-labelled ginsenosides.
B. 1. 3. synthesized ^{14}C-labelled ginsenosides. 2. standard ginsenosides Rb_1, Rb_2, Rc, Rd, Rg_1.

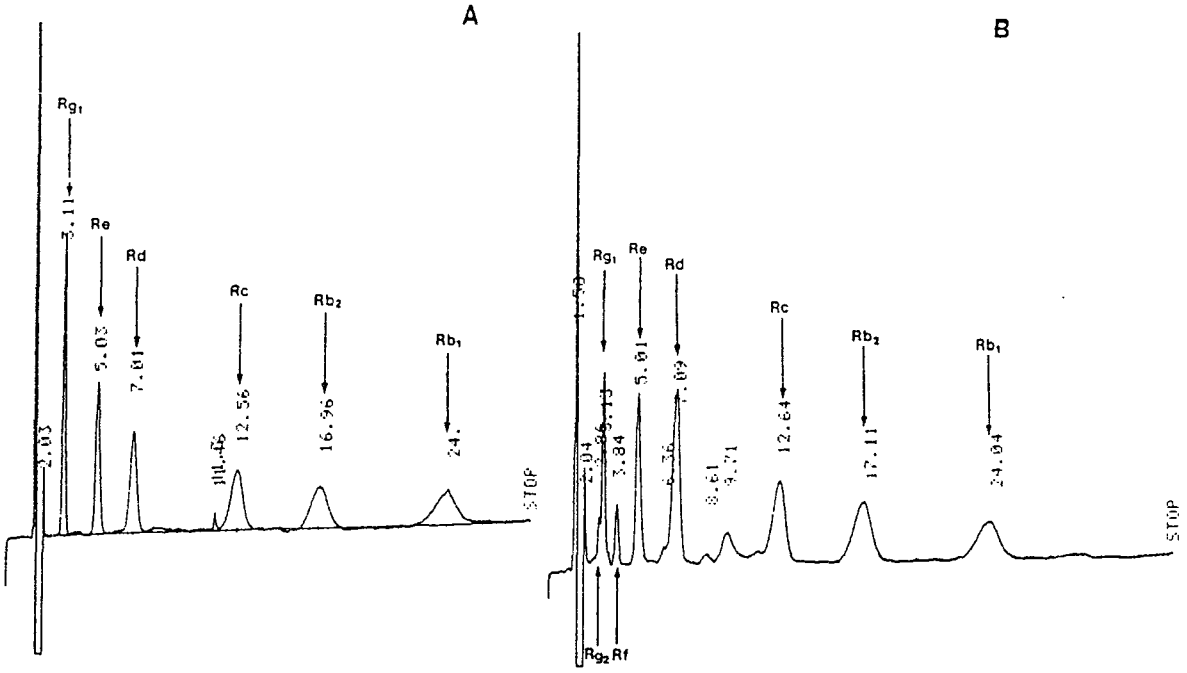

Fig. 1-b. Chromatograms of ^{14}C-labelled ginseng saponins (B) prepared from [U-^{14}C] acetate and natural saponins (A) from the roots of *Panax ginseng C. A. Meyer*. HPLC was conducted using μ-Bondapak NH_2 column [solvent system ; acetonitrile-H_2O-BuOH, 80 : 20 : 15(v/v/v), detector ; RI, chart speed ; 1cm/min, flow rate ; 1.0mℓ/min].

ginsenosides. We obtained relatively large amounts of radioactive TLC pure ginsenoside Rg_1 and a little radioactive ginsenoside Rb_1 by silica gel column chromatohraphy.

Mice(ICR) were fed orally with 1mg of ^{14}C-ginsenosides Rg_1 and natural pure Rg_1 mixture per mouse. And the liver, brain, small and large intestine, blood from artery, urine and feces were assayed on time course after the feeding. As shown in Table 2, the highest radioactivities recovered from liver and small intestine were found both at 3 hrs and that of large intestine was at 5 hrs after the feeding. The recovered radioactivities from urine and feces were gradually increased as the time elapsed. Although the highest radioactivity of the liver appeared at 3 hrs after the feeding, radioactivity of butanol extract of the liver was highest not at 3 hr. but at the right begining after the feeding and the radioactivity decreased gradually as the time elapsed, suggeting that ginsenosides were metabolized(Table 3).

Primary culture of rat liver cells in the medium containing radioactive ^{14}C-ginsenoside Rg_1 showed that the radioactivity in butanol extract(ginsenosides) was 20% and those of lipid fraction (ethyl ether extract) and residues(mainly sugar)were 23.1% and 16.1% respectively(Table 4-a). Detailed examination of the chromatogram of butanol extract showed that only 17.5% of originally added ginsenoside remained unchanged and the rest was transformed as shown in Table 4-b. Other ginsenosides such as Rb_1, Rb_2+Rc mixture and Rd+Re mixture were also changed. Fig. 2 showed the autoradiogram of butanol extract of rat hepatocytes cultured for 24 hr in the media containing ^{14}C-labelled ginsenosides such as Rg_1, Rb_1, Rb_2+Rc mixture and/or Rd+Re mixture.

Table 3. Recovered radioactivity of ginsenosides from mouse liver homogenate on time course after the oral administration of 1mg of radioactive ginsenoside $Rg_1$0.698μCi/mg/mouse).

Time(hr)	Radioactivity(cpm)				
Fraction	1	3	5	12	24
Liver homogenate	35,100	84,180	44,400	31,440	19,500
Ginsenoside fraction	22,400	17,200	5,900	2,900	3,400
Relation(%)	63.82	20.43	13.29	9.22	17.44

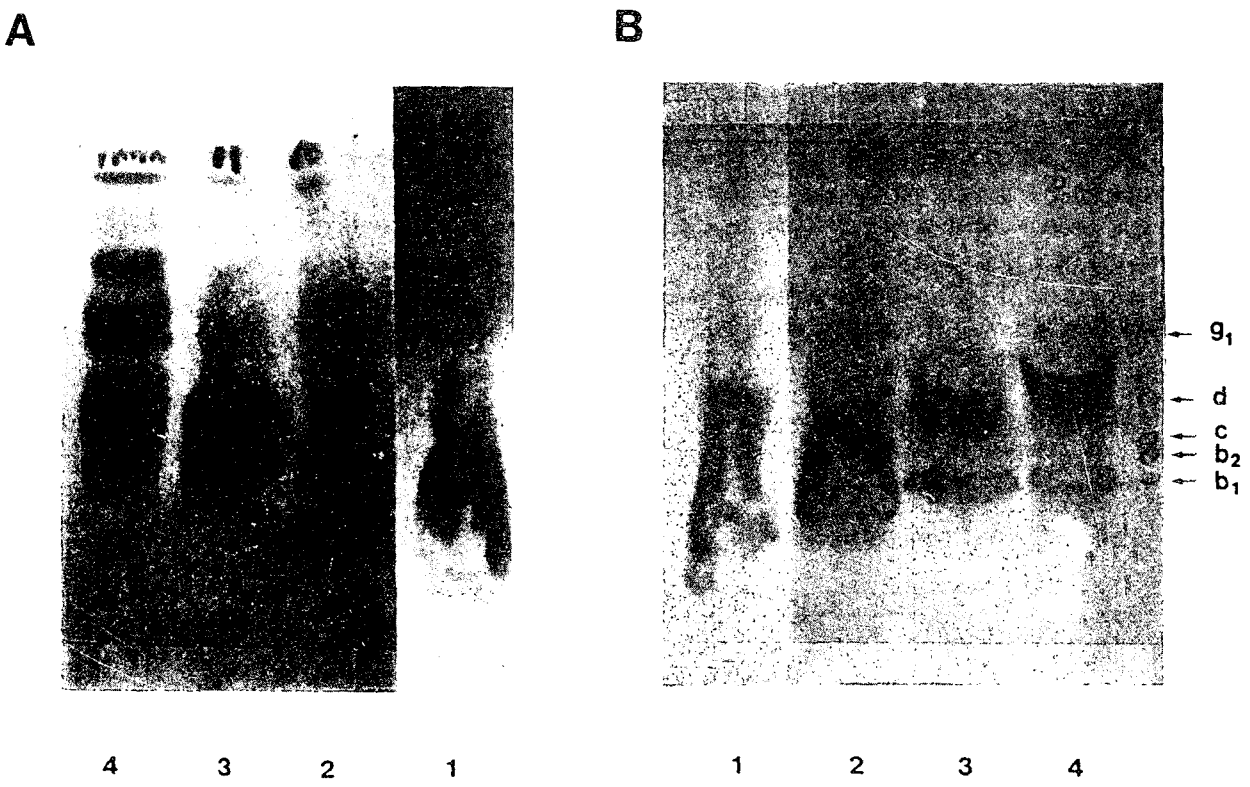

Fig. 2. Autoradiogram of butanol extract of rat hepatocytes cultured for 24 hours in the medium containing different ^{14}C-labelled ginsenoside such as 1 : Rb_1, 2Rb_2 : Rc, 3Rd+Re and 4 : Rg_1.
A. Autoradiogram. B. H_2SO_4 charling.

Table 4. Radioactivity distribution in varouss extracts(a) and silica gel thin layer chromatogram(b) of the butanol extract of rat hepatocytes cultured(24 hrs) in the medium containing radioactive ginsenoside Rg_1.

(a)

Added ginsenoside in the medium (cpm)	Radioactivity(cpm) (% recovered) Ethyl ether extract (Lipid fraction)	BuOH extract (Saponin fraction)	Residue (mainly sugars)
6×10^5	1.39×10^5 (23.1)	1.2×10^5 (20.0)	9.7×10^4 (16.1)

(b)

Recovered radioactivity (cpm) from the position of corresponding individual ginsenosides and sapogenin on thin layer chromatogram.

Ro+Ra	Rb_1	Rb_2+Rc	Rd+Re	Rf	Rg_1	Sapongenin
255	516	606	2,282	1,102	1,694	3,178
(2.63)	(5.32)	(6.25)	(23.53)	(11.36)	(17.46)	(32.76)

The figures in bracket are relavive % assuming the total radioactivity being 100.

Ginsenoside mixture extracted from dried roots of panax ginseng was mixed with the synthesized ^{14}C-ginsenosides and then fractionated by HPLC and the individual ginsenosides were estimated from the peak area of the corresponding fractions(Table 5). The amounts of individual ginsenosides in blood and liver after the oral administration of the above ginsenoside mixture were also analyzed and found that the absorbed amounts of individual ginsenosides were different from one another(Table 6). Previous work in this laboratory showed that half lives of ginsenosides were estimated to be around 5 hours(Lee and Joo, 1983). This and above data suggest that the ginsenosides are absorbed partly in an undissociated form and the ginsenoside level in the liver might be maintained at $10^{-6}\sim10^{-5}$% for a considerable period of time after administration.

We have investigated the effect of ginsenosides on various enzyme reactions *in vitro* and realized that moderate amounts of ginsenosides(10^{-6}%$\sim^{-4}$% in the reaction mixture) stimulated most enzyme reactions nonspecifically so far tested in this laboratory. The Michaelis constants(Km) of various enzymes for their substrates lowered in the presence of moderate amounts of ginsenosides. UV difference spectra, CD spectra, eletrophoretic mobilities, DTNB titration and substrate binding data demonstrated that moderate amounts of ginsenosides might bring about a slight change of the enzyme conformation which would be in favour for the enzyme reactions being proceeded. Other amphiphiles such as Triton X-100 and deoxycholate also showed a similar behaviour as ginsenosides. The effects of several amphiphiles including ginsenosides on several enzymes such as porcine pancreatic lipase and succinate dehydrogenase were examined and found that optimal concentrations of the amphiphiles for maximum enzyme activity were found to be an almost same range(10^{-4}%$\sim10^{-3}$%) suggesting that the surface activity of ginsenosides might play

Table 5. Radioactivities of individual ginsenosides of the mixture of natural ginsenosides prepared from panax ginseng roots and synthesized ^{14}C-ginsenosides. Individual ginsenosides were fractionated by HPLC and the amounts were estimated from the peak of the corresponding ginsenosides.

Fraction	Amounts(μg)	Radioactivity(DPM)	Specific radioactivity (DPM/mg)
Rg_2, Rg_1 and Rf	110	566,131	5,146
Re	102	137,155	1,344
Rd	94	2,321,770	23,935
Rc	165	42,867	260
Rb_2	97	409,940	4,226
Rb_1	110	67,633	614
Rh_1, Ra, Ro and others	—	—	—
Total	1,000	5,600,000	5,600

Table 6. Ginsenoside levels of bolld serum and liver of rat after the oral administration of 1㎎ of the mixture of natural ginsenosides and synthesized ^{14}C-ginsenosides(5.6×10^6 ppm). Individual ginsenosides were fractionated by HPLC and the amounts were calculated from the radioactivities of corresponding fractions.

Fraction	administered amount(㎍)	Blood serum		
		Recovered ginsengside(ng)	% recovered	ginsenoside level($\times10^{-5}$%)
Rg_2, Rg_1 and Rf	110	28 ± 1.55	0.025	0.22
Re, Rd	196	720 ± 34.06	0.367	5.54
Rc	165	1,640 ± 61.91	0.994	12.60
Rb_2	97	370 ± 18.03	0.381	2.84
Rb_1	110	102 ± 6.19	0.093	0.78

Fraction	administered amount(㎍)	Liver					
		1hr.			4hr.		
		Recovered ginsenoside(ng)	Recovered %	ginsenoside level(10^{-5}%)	Recovered ginsenoside(ng)	Recovered %	ginsenoside level(10^{-5}%)
Rg_2, Rg_1 and Rf	110	160 ± 9.28	0.145	0.29	68.11 ± 0.11	0.062	0.13
Re, Rd	196	1,270 ± 37.15	0.647	2.37	27.86 ± 0.84	0.014	0.06
Rc	165	2,700 ± 12.38	1.636	5.02	334,86 ± 4.36	0.202	0.65
Rb_2	97	148 ± 6.19	0.153	0.27	6.19 ± 0.91	0.006	0.01
Rb_1	110	360 ± 9.30	0.327	0.67	27.86 ± 0.61	0.025	0.06

a significant role in enzyme catalyzed reactions(Kim *et al.*, 1985 ; Kim and Joo, 1985 ; Joo, 1976).

Ethanol is one of the favorite mood-altering drug and its psychic effects, both pleasant and unpleasant, are well known, but its overconsumption taxes the body's economy, produced a number of pathological changes, particularly in the liver and impairs biological functions. Present knowledge on alcohol metabolism showed that over-consumption of alcohol causes cirrhosis and death not only because alcoholism promotes malnutrition but also because the excess amount of hydrogen and acetaldehyde are produced during ethanol oxidation(Joo, 1984).

Rats were fed with 12% ethanol with/without 0.1% ginsenoside mixture instead of water for 6 days and acetaldehyde level of ethanol fed group was much higher than normal group. However, that of ethanol-ginsenoside fed group was decreased appreciably(Table 7). The decrease of [NAD^+] / [NADH] ratio in the liver of ginsenoside fed group was also significantly smaller than non-ginsenoside fed group(Table 8). Radioisotope distribution of hepatic lipids at 30 min after the intraperitoneal injection of [1-^{14}C]-ethanol revealed that total radioactivity of hepatic lipids of ginsenoside fed group was greatly lower than non-ginsenoside fed group. Results of lipid analyses demonstrated that the depression of phospholipid

Table 7. The amount of acetaldehyde in the liver of fed with 12% ethanol and 0.1% ginsenoside mixture for 6 days prior to the intraperitoneal injection of 10% ethanol(1㎖). The rats were killed at 30 min. after the ethanol injection.

Group	Liver (nmole/g liver)
Normal	210.7 ± 98.6 (100)
Ethanol fed	304.7 ± 119.5 (145)*
Ethanol and ginsenoside fed	238.3 ± 24.5 (113)*

Numbers in brackets are the relative ratios that were expressed assuming that of normal being 100.
*$p<0.05$

Table 8. [NAD$^+$]/[NADH] ratio in the liver of rat fed with ordinary diet and 12% ethanol along ith(test) and/or without(control) 0.1% ginsenoside mixture instead of water(free access) for 6 days. Normal group was fed only ordinary diet and water.

		Normal	Control	Test
[NAD$^+$]/[NADH]	Cytosol	866	507	676
	Mitochondria	7.58	4.68	6.12

biosynthesis and the increase of fatty acid/triglycerides caused by ethanol feeding were appreciably normalized by the co-feeding of gisenoside supplement(Table 9).

Rats(150~200g, male) were given freely with 12% ethanol(Control) and/or 12% ethanol containing 0.1% natural ginsenoside mixture(test) instead of water for 6 days and the liver was analyzed. As shown in Table 10, ALDH activities of both control and test group were lower than that of normal group but ALDH of test group was less inhibited than control. Electron micrograph showed that severely swollen and disrupted mitochondrial and dilated or vesiculated ER are very few and swollen or disrupted mitochondria can not be seen(Table 11). From the above experimental results, it seemed that ginsenoside might stimulate the removal of acetaldehyde and excess hydrogen formed during the ethanol oxidation, resulting in the decrease of their toxicity.

It was demonstrated in this laboratory that ginsenosides have some preventive effect against hypercholesterolemia induced by prolonged high cholesterol diet administration in rabbits(Joo, 1980) and rats (Joo *et al.*, 1987). Cholesterol is transported in the plasma in macromolecules called lipoproteins, which consist of various amounts of specific proteins, cholesterol, cholesterol esters, triglycerides and phospholipids. The importance of low density lipoprotein(LDL) recep-

Table 9. Distribution of radioactivity(DPM) of hepatic lipids of the rat fed with [1-^{14}C]-ethanol. The rats were killed at 30 min. after the intraperitoneal injection of ethanol. The control and test groups were fed with 12% ethanol or 12% ethanol containing 0.1% ginsenoside mixture respectively, instead of water for 6 days prior to the injection of labelled ethanol.

Lipid fraction	Radioactivity(DPM)		
	Normal	Control	Test
Total lipid	114,089(100)	176,867(100)	142,637(100)
Phospholipid fraction	49,045(43.0)	12,407(7.0)	34,322(24.1)
Cholesterol fraction	10,528(9.2)	10.248(5.8)	10.267(7.2)
Fatty acid fraction	22,895(20.1)	49,820(28.2)	47,119(33.0)
Triglyceride fraction	35,817(31.4)	73,141(41.4)	59,326(41.6)

Table 10. The effect of ginsenosides on ADH, ALDH and MEOS in prolonged ethanol fed rats *in vivo*. The rats were fed with 12% ethanol(control) and/or 12% ethanol containing 0.1% ginsenoside mixture(test) instead of water for 6 days.

Group	ADH (uni(a)/mg protein)	ALDH (uni(a)/mg protein)	MEOS (uni(a)/mg protein)
Normal	8.743 ± 0.159 (100)	3.076 ± 0.600 (100)	3.165 ± 0.472 (100)
Control	10.136 ± 0.221 (116) *	2.303 ± 0.661 (75) *	4.443 ± 0.681 (140) *
Test	9.242 ± 0.123 (106)	2.678 ± 0.015 (87) *	7.028 ± 0.775 (222) *

Figures in brackets are relative activities assuming that of control being 100.
a) One unit of enzyme was defined as one nmole of NADH formed per min.
b) One unit of enzyme was defined as one μmole of aceta
*$p<0.05$

Table 11. Electron microscopic observation of the effect of ginsenosides on hepatocytes of rats dosed with 12% ethanol instead of water for 6 days.

Group		Sweling & disruption of mitochondria	Dilataion & vesi- of RER	Proliferation of SER	Pyknosis	Fat deposition
Control	1	+++	+++	+++	+	++
	2	+++	+++	+++	+	+++
	3	+++	++	++	+	++
	4	++	+++	++	+	++
	5	++	+++	++	+	++
Test	1	−	+	+	−	−
	2	−	−	−	−	+
	3	−	−	−	+	−
	4	+	+	−	−	+
	5	+	−	−	−	−

Control group was fed with 12% ethanol only instead of water for 6 days. Test group was fed with 0.1% ginsenoside mixture in 12% ethanol instead of water.
− : normal, + : mild, ++ : moderate, +++ : servere

tor is highlighted by studies of familial hypercholesterolemia. Cholesterol is deposited in various tissues because of the high concentration of LDL−cholesterol in the plasma.

^{125}I−LDL was injected intravenously to rabbits which had been fed with high cholesterol diet with and/or without ginsenosides for 12 days and found that the radioactivity disappearance from ginsenoside fed group was faster than from non-ginsenoside fed group as shown in figure 3. The binding activity of ^{125}I−LDL to rabbit liver plasma membrane of ginsenoside fed group was higher than non-fed group as shown in figure 4.

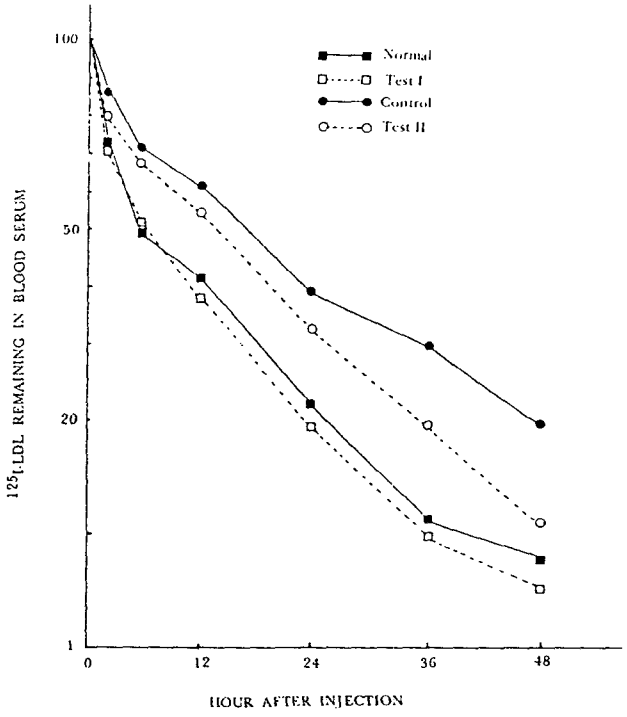

Fig. 3. Effect of ginseng saponin on ^{125}I-LDL removal from the blood serum of normal diet fed rabbits(normal), normal diet and ginseng saponin fed rabbits(test I), high cholesterol diet fed rabbits(control) and high cholesterol diet and ginseng saponin fed rabbits(test II) for 12 days.

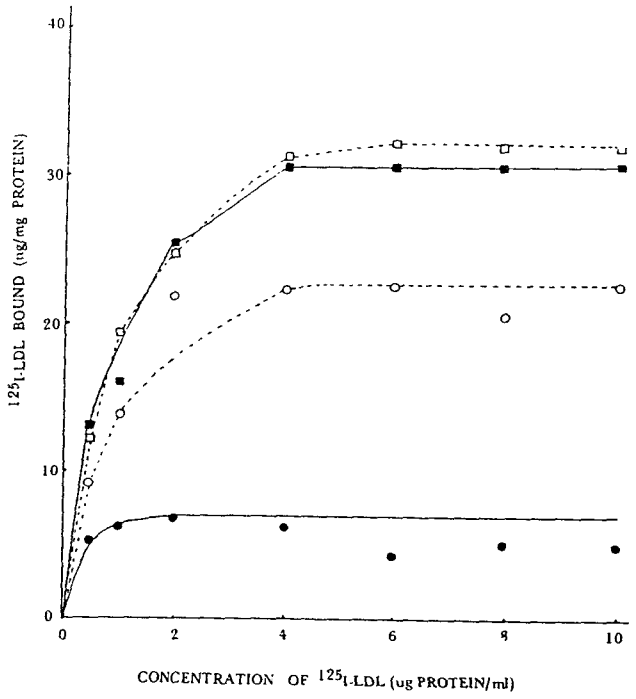

Fig. 4. Binding of rabbit ^{125}I−LDL to EDTA−sensitive binding sites of liver membranes of normal diet fed rabbits(normal : ■—■), normal diet and ginseng saponin fed rabbits(test I : □----□), high cholesterol diet fedrabbits(control : ●—●) and high cholesterol diet and ginseng saponin fed rabbits(test II : ○----○) for 12 days.

To understand the possible mechanism of the preventive action, against hypercholesterolemia, LDL - receptor binding, cholesterol level, and cAMP level of chinese hamster ovary (CHO) cells cultured under different conditions were examined.

When LDL(20μg/mℓ) was added to the culture medium, LDL receptor binding is usually supressed down to almost half that of normal group. However, ginsenosides at 10^{-2}% and 10^{-3}% (w/v) in the medium exerted an appreciable stimulatory effect on the LDL - receptor binding(Fig. 5). Ginsenosides also reduced the elevated cholesterol level almost down to a normal group(Table 12). Furthermore, ginsenosides increased intracellular cAMP level, which is almost half of the normal group due to the presence of LDL in the medium(Table 13). Comparison of K_d and V_{max} value for LDL binding to the receptor suggested that the observed stimulation is related to the receptor pupulation, not to the binding affinity(Table 14).

The bile acids into which most of the cholesterol is converted are secreted into the upper intestine, where they emulsify dietary fats. Having done their work, the bile acids are largely reabsorbed from the intestine, taken up by the liver and again secreted into the upper intestine. This enterohepatic circulation of bile salts ordinary limits the liver's need for cholesterol. Therefore, if the recycling could be in-

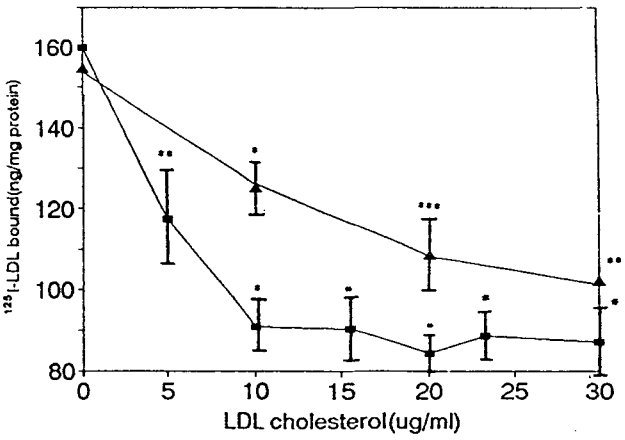

Fig. 5. The effect of various LDL concentration in the medium on LDL receptor activity in CHO cells and the modulatory effect of ginsenoside on the suppression by LDL. CHO cells were cultured for 48h. in serum free medium containing various concentration of LDL cholesterol in the presence(▲) or absence(■) of 10^{-3}% (w/v) ginsenoside. The results are the mean values of five determinants for each point.
•p<0.001 : ••p<0.01 : •••p<0.02

Table 12. The effect of various concentraions of ginsenosides on cholesterol concentration in CHO cells.

Group	Cholesterol (μg/mg protein)	Relative (%)
Normal	59.8 ± 7.0*	100
Control	78.1 ± 8.4	130
Saponin 10^{-2}%	74.7 ± 4.4	125
Saponin 10^{-3}%	68.6 ± 10.8	115
Saponin 10^{-4}%	61.0 ± 6.4*	102
Saponin 10^{-5}%	68.4 ± 3.5**	114

Normal group was cultured in serum free medium, and control group was cultured in serum free medium containing 20μg/mℓ LDL cholesterol for 48h. Test groups were cultured for 48h in serum free medium containing 20μg/mℓ LDL cholesterol and different concentrations of ginsenoside mixture. The values are the mean value of five determinants.

Table 13. The effect of ginsenoside on cAMP concentration in CHO cells cultured under various conditions.

Group	cAMP (pmole/mg protein)	Relative (%)
Normal	46.5 ± 9.98	100
Control	25.8 ± 1.6	55.5
Saponin 10^{-2}%	29.0 ± 4.9	62.4
Saponin 10^{-3}%	33.4 ± 2.5 *	71.8
Saponin 10^{-4}%	27.7 ± 1.6	71.8

Normal group was cultured in serum free medium, and control group was cultured in serum free medium containing 20μg/mℓ LDL cholesterol for 48h. Test groups were cultured for 48h in serum free medium containing 20μg/mℓ LDL cholesterol and different concentrations of ginsenoside mixture. The values are the mean value of five determinants.
•p<0.01

Table 14. The comparison of K_d and B_{max} value.

Group	B_{max} (μg LDL bound/mg protein)	K_d (μg LDL/mℓ)
Normal	1530	12.9
Control	1210	13.9
Test	1390	13.9

Normal group was cultured in MEM−0%, control group was cultured in MEM−0% containing 20μg/mℓ LDL cholesterol, and test groups was cultured in MEM−0% containing 20μg/mℓ LDL cholesterol plus 10^{-2}% ginsenoside mixture. Their binding abilities were assayed under different concentrationof of ^{125}I−LDL.
concentrations of ginsenoside mixture. The values are the mean value of five determinants.

terrupted, the liver would be called on to convert more cholesterol into bile acids and this should lead the liver cells to make more LDL receptors. We have observed that the addition of ginsenoside(10^{-2}%) decreased the uptake of taurocholic acid as much as 20% at the actively trasporting everted ileal sacs(Fig. 6) , but it failed to form a large mixed micelles with taurocholic acid, which was one of the proposed mechanisms by which ginsenoside inhibits bile acid reabsorption(Table 15). From the above results, it seemed likely that ginsenoside prevented hypercholesterolemia by decreasing cholesterol level in cells thereby relieving the inhibition of LDL receptor synthesis by cholesterol and also by inhibiting

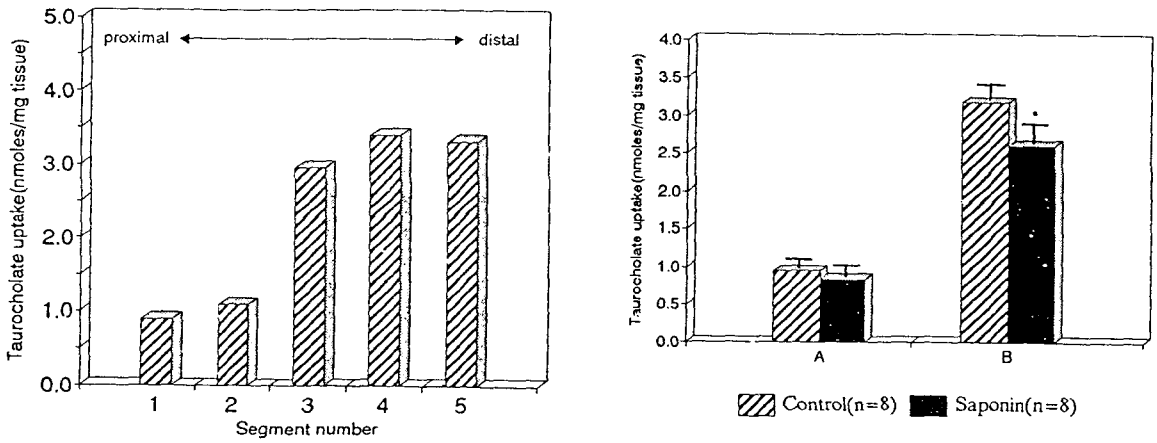

Fig. 6. (A) Transport of taurocholic acid by various segments of the rat small intestine(Everted sacs were incubated in 0.2mM taurocholic acid in Krebs−Ringer bicarbonate buffer at 37℃ for 90 min. constantly gassed with 95% O_2, 5% CO_2. Segment 1 and 2 were obtained from jujenum and segment 3, 4, and 5 were from ileum)
(B) The effect of ginsenoside(10^{-2}%) on taurocholic acid uptake by rat small intestine sacs. The bars represent the mean value of eight determinants
A : everted sacs of rat jujenum ; B : everted sacs of rat ileum *$p<0.01$.

Table 15. The effect of ginsenosides on bile acid micelle fromation.

Group	A(mM)	B(mM)
Normal	0.071	0.57
Saponin 10^{-2}%	0.068	0.05
Saponin 10^{-3}%	0.067	0.55
Saponin 10^{-4}%	0.068	0.54

A : Concentration of taurocholic acid in 10mℓ of outer solution after 36 h dialysis of 5mℓ of 0.2mM taurocholic acid solution with stated amount of ginsenoside at 37℃.
B : Concentration of taurocholic acid in 10mℓ of outer solution after 36 h dialysis of 5mℓ of 2mM taurocholic acid soultion with stated amount of ginsenoside at 37℃.

Table 16－a. The effect of ginsenosides on blood serum composition and the amount of glycogen and several enzyme activities of the liver of streptozotocin induced diabetic rats. Values are expressed as percent assuming that of the corresponding normal level being 100.

Serum composition/ enzymes	Streptozotocin injected	Streptozotocin+ saponin mixture injected rats	Streptozotocin+ ginsenoside Rb_1 injected rats	Streptozotocin+ ginsenoside Rb_2 injected rats
*Phosphofructokinase	64.0	86.7	89.3	98.7
Pyruvate kinase	45.6	66.4	39.9	64.7
*G－6－P dehydrogenase	34.6	85.2	57.2	81.6
6－Phosphogluconate dehydrogenase	51.3	90.0	85.6	96.2
Malic enayme	67.9	78.5	68.6	68.7
*Glucokinase	42.6	115.2	107.4	105.3
G－6－phosphatase	195.0	164.2	159.8	163.7
Glycogen phosphorylase	30.0	57.6	34.5	21.0
*Glycogen	41.3	78.4	68.8	79.8
*Acetyl CoA carboxylase	33.3	146.0	79.0	130.3
*Glucose	488.9	122.2	113.6	169.2
*β－Hydroxybutyrate	158.0	79.7	59.4	59.4
*Acetoacetate	339.8	237.9	228.2	233.0
*Lactate	136.4	62.6	87.5	100.3
*non－Esterified fatty acid	184.6	149.5	153.2	154.2
*Triacylglycerol	244.2	72.3	63.9	117.6

* statistically effective

Table 16－b. The effect of ginsenosides on blood serum composition and the amount of glycogen and several enzyme activities of the liver of normal rats. Values are expressed as percent assuming that of the corresponding normal level being 100.

Serum composition/ enzymes	Saponin mixture injected rats	Ginsenoside Rg_1 injected rats
Phosphofructokinase	98.7	100.0
Pyruvate kinase	101.2	100.6
G－6－P dehydrogenase	115.2	130.2
6－Phosphogluconate dehydrogenase	108.4	134.5
Malic enayme	92.0	86.0
Glucokinase	114.3	102.0
G－6－phosphatase	94.2	92.7
Glycogen phosphorylase	95.7	107.2
Glycogen	90.9	82.7
Acetyl CoA carboxylase	282.0	234.5
Glucose	105.8	113.5
β－Hydroxybutyrate	63.0	80.0
Acetoacetate	165.0	141.7
Lactate	95.0	83.0
non－Esterified fatty acid	102.8	112.1
Triacylglycerol	94.0	11.1

bile acid reabsorption from the samall intestine.

Increased levels of glucose, ketone bodies, non - esterified fatty acids, lactate in blood, and a decreased glycogen level ot the liver and enzymes involved in carbohydrate and lipid metabolism such as phosphofructokinase, glucokinase, glucose - 6 - phosphate dehydrogenase, 6 - phosphogluconate and acetyl CoA carboxylase of streptozotocin induced diabetic rats were significantly modified by intraperitoneal injection of ginsenoside mixture and/or purified ginsensode(Table 16). Taken together these results, it is postulated that the hypoglycemic action of ginsenosides is not due to their direct action on enzyme activities, since the saponin effect of several enzymes *in vitro* was not enough to explain such an appreciable hypoglycemic activity of ginsenosides in streptozotocin induced diabetic rats(Table 17).

Table 17. The effect of ginsenosides on several enzymes relating carbohydrate metabolism and fatty acid biosyn thesis *in vitro*. The concentration of ginsenoside mixture in the corresponding enzyme assay mixture was 10^{-4}%. Values are the mean value of three determination.

Enzyme	Relative activity(%)
Glucose - 6 - phosphatase	113.4 ± 2.38
Glucokinase	111.4 ± 1.50
Phosphofructokinase	128.0 ± 3.09
Glucose - 6 - phosphate dehydrogenase	110.8 ± 2.78
Malic enzyme	114.6 ± 2.78
Acetyl CoA carboxylase	135.8 ± 3.51

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