

## ENDOCRINOLOGICAL AND METABOLIC ACTIONS OF GINSENG PRINCIPLES

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It is my great honor to be invited to this symposium and present the paper again. At the first International Ginseng Symposium and International Symposium on Gerontology in Lugano, Yamamoto, Kumagai and Yamamura reported that ginseng principles and ginsenosides had the stimulatory actions of bone marrow cells and testes where cell division is very active. Synthesis of DNA, RNA, protein and lipid was increased with decreased cyclic AMP and increased cyclic GMP. Blood-making and tonic actions of ginseng may be partially explained by these data (Table 1).<sup>1) 2) 3)</sup>

We have studied the mechanism of actions of hormones and drugs affecting lipid metabolism in relation to atherosclerosis since nearly 20 years. Pathogenesis of atherosclerosis has made considerable progress recently.

Part one of this report is about effects of ginseng principles on lipid metabolism and atherosclerosis. Male rats of Sprague-Dawley strain were used. Plasma cholesterol and triglyceride levels of rats fed a 1% cholesterol-0.5% cholic acid diet for 7 days were both high, but the intramuscular injections of either of ginseng saponins (fraction 4), saikosaponins or glycyrrhizin reduced plasma lipid levels (Fig 1).<sup>4)</sup>

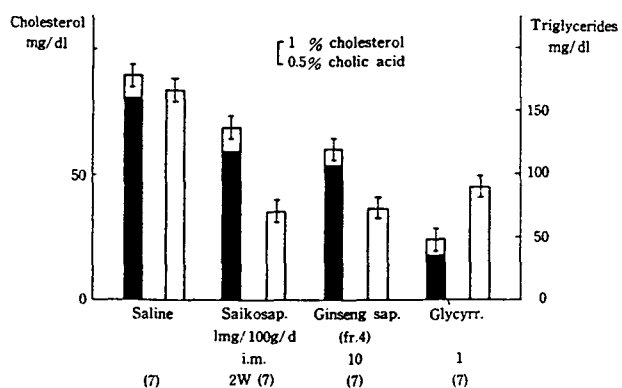
Radioactivity of cholesterol remained 48 hours after intraperitoneal injection of 4-(<sup>14</sup>C) cholesterol. The plasma of rats administered with ginseng

**Table 1**

Actions of ginseng saponins	
Bone marrow	
DNA synthesis	↑
RNA synthesis	↑
Protein synthesis	↑
Lipid synthesis	↑
cAMP content	↓
cGMP content	↑
Mitosis	↑
Testes	
DNA synthesis	↑
Protein synthesis	↑
Ascites hepatoma	
DNA synthesis	~
Protein synthesis	~
Lipid synthesis	~
Lipid metabolism	
Plasma cholesterol, TG, PL & NEFA levels (tumor-bearing; high chol, diet-fed)	↓
Cholesterol synthesis in liver	↑
Fatty acid synthesis in liver and ad. tissue	↑
TG acid synthesis in liver and ad. tissue	↑
Excretion of bile acids and sterols into feces	↑
Cholesterol turnover in plasma	↑
Adipose tissue (normal, tumor-bearing)	
Lipolysis	↓
Lipogenesis	↑

saponins was significantly lower than controls (Table 2).<sup>4)</sup>

Fecal excretion of radioactive bile acids and sterols after intraperitoneal injection of 4-(<sup>14</sup>C) cholesterol was accelerated by ginseng saponins.



**Fig. 1.** Effect of saikosaponins, ginseng saponins and glycyrrhizin on plasma lipid levels of rats fed a high cholesterol diet.

(Table 3) These results may suggest that ginseng principles accelerated cholesterol turnover and reduced plasma cholesterol level.<sup>4)</sup>

To check the net effect of ginseng, effects of oral administration of red ginseng powder for 90 days on plasma lipids, lipid peroxide, platelet adhesiveness and atherosclerosis, were investigated using rats fed a high cholesterol-diet (Table 4). Red

**Table 2.** Effect of ginseng saponins on elimination of intraperitoneally injected cholesterol-4-<sup>14</sup>C from plasma

Cholesterol-4- <sup>14</sup> C	No. of rats	0.5 $\mu$ Ci/100g b.w. Radioactivity 48 hrs after <sup>14</sup> C injection dpm/ml plasma
Control	5	11,200 $\pm$ 760
Ginseng ext. fr.4 i.m. inject. 10mg/100g b.w./d. 7 d.	5	7,650 $\pm$ 480

p < 0.01

ginseng powder used was manufactured at Office of Monopoly, Republic of Korea. Total cholesterol, triglyceride, NEFA and total cholesterol-HDL-cholesterol/ HDL-cholesterol, i.e., so called atherogenic index, were much decreased, while HDL-cholesterol and phospholipid were significantly increased. Lipid peroxide remained unchanged. Platelet adhesiveness was decreased (Table 5).

Fatty liver induced by high cholesterol-diet feeding was improved by simultaneous oral administration of red ginseng powder. Hepatic total cholesterol and triglyceride were decreased, while phospholipid and NEFA were increased (Table 6).

**Table 3.** Effect of ginseng on saponins fecal excretion of intraperitoneally administered cholesterol-4-<sup>14</sup>C

Group	No. of rats	Excretory rate of injected cholesterol-4- <sup>14</sup> C** into feces for 48 hrs as: (%)			
		Total <sup>14</sup> C	Bile acids	Non-sapon.	7 $\beta$ -OH-sterols
Control	5	21.6 $\pm$ 2.1*	10.4 $\pm$ 1.3*	6.8 $\pm$ 0.6	4.9 $\pm$ 0.4
Ginseng ext. fr. 4 i.m. injected 10 mg/100g b.w. 7d.	3	37.7	20.3	16.0	11.5
Rate of increase by ginseng treatment (control: 1)		1.7	2.0	2.4	2.3

\*Mean  $\pm$  standard error. \*\*0.5  $\mu$ Ci/100g b.w.

**Table 4.** Effect of ginseng powder on plasma lipids and lipid peroxide of high cholesterol diet-fed rats

Description	Unit	Control	Ginseng*
Total cholesterol (TC)	mg/dl	93.6 + 14.6**	64.7 + 3.3*****
HDL-cholesterol (HDL-C)	mg/dl	24.9 + 2.8	31.7 + 2.6****
TC-HDL-C/HDL-C		3.0 + 0.5	1.1 + 0.1*****
Triglyceride	mg/dl	230 + 35	161 + 15****
NEFA	uEq/l	1207 + 76	980 + 39****
Phospholipid	mg/dl	135 + 6	148 + 5****
Lipid peroxide	nmol/ml	8.0 + 0.4	8.0 + 0.4***

\* Ginseng powder: 100 mg/100 g b. w./d. p.o. 90 days

\*\* Mean + S.E.

\*\*\* N. S.: Non-significant, \*\*\*\*P < 0.05 \*\*\*\*\*P < 0.01

\*\*\*\*\*P < 0.001

**Table 5.** Effect of ginseng powder on platelet adhesiveness of high cholesterol diet-fed rats

Control	63 + 5*
Ginseng	37 + 4**

\* Mean + S.E. \*\*P < 0.05  
Ginseng: Red ginseng powder 100 mg/100g b.w./day, p.o. 90 days platelet adhesiveness: Saizman method.

**Table 6.** Effect of ginseng principles on hepatic lipids of high cholesterol diet-fed rats

		Control	Ginseng*
Total cholesterol	mg/dl	72 + 6**	50 + 4****
Triglyceride	mg/dl	124 + 12	72 + 7****
NEFA	uEq/l	608 + 36	887 + 35****
Phospholipid	mg/dl	109 + 5	128 + 4****

\* Ginseng powder: 100 mg/100 g b.w./day., p.o. 90 days  
\*\* Mean + S.E. \*\*\*N.S.: Non-significant  
\*\*\*\* P < 0.05 \*\*\*\*\*P < 0.01 \*\*\*\*\* < 0.001

Macroscopically color of the liver was quite different between the cholesterol diet-fed and the cholesterol plus ginseng diet-fed, that is, yellow in the former and red in the latter. Histological examinations revealed that fatty infiltration was improved by ginseng administration.

It is reported that plasma lipid levels of tumor-bearing animals were enhanced. We have observed that the high cholesterol, triglyceride, phospholipid and NEFA levels in ascites hepatoma-

bearing rats were reduced by administration of ginseng saponins. (Table 7)<sup>5</sup> Synthesis of phospholipid, cholesterol and triglyceride from 1-[<sup>14</sup>C] acetate in the liver of tumor-bearing and normal rats was increased by ginseng saponins in vivo. (Table 8). The same effect was observed in vitro experiment. Synthesis of total lipids and fatty acids was increased in adipose tissue of normal and tumor-bearing rats by ginseng saponins in vivo (Table 9). Also the same effect was observed in vitro experiment.

Saito, Matsuoka, Yamamoto, Kumagai and Okuda reported that ginsenosides reduced ACTH-induced lipolysis and enhanced lipogenesis in fat cells. Ginseng might have insulin-like action. Ginseng saponins may stimulate lipoprotein lipase and inhibit hormone-sensitive lipase.<sup>6</sup>

Part two of this report is about effects of ginseng principles on hormone secretion. It is conceivable that ginseng principles might have both hormone-like metabolic actions and regulatory actions of hormone secretion. We investigated the effects of single and one week administrations of red ginseng powder or saponins on plasma levels of various hormones and lipids in 8 normal volunteers and 3 diabetic patients. Single administration reduced plasma glucose (Table 10). Both plasma immunoreactive insulin and glucagon remained unchanged.

**Table 7.** Effect of oral administration of ginseng principle fraction 3 on plasma lipid levels in the tumor-bearing rats

	Number	Cholesterol mg/dl	Triglyceride mg/dl	Phospholipid mg/dl	NEFA mg/dl
Non-tumor-bearing					
Normal diet	12	59.9 + 3.5	84.1 + 5.9	92.5 + 6.7	631 + 66*
Ginseng diet**	12	64.8 + 5.8	87.6 + 4.7	103.8 + 9.4	640 + 47
AH 130 hepatoma-bearing***					
Normal diet	12	145.2 + 6.9	184.4 + 13.6	126.2 + 7.5	1389 + 103
Ginseng diet	12	119.3 + 8.8	130.2 + 7.1	117.9 + 8.5	999 + 130
AH 41C hepatoma-bearing (I)***					
Normal diet	12	98.9 + 7.2	95.0 + 7.5	109.6 + 5.2	971 + 118
Ginseng diet	12	77.4 + 8.1	71.3 + 5.9	94.0 + 3.7	813 + 89
AH 41C hepatoma-bearing (II)***					
Normal diet	12	116.1 + 7.4	129.4 + 8.5	117.4 + 5.3	1123 + 63
Ginseng diet	12	97.4 + 6.1	86.8 + 6.3	107.2 + 6.2	837 + 52
		††	‡‡‡	††	‡‡‡

\* Mean + S.E. \*\*1 mg/100 g body weight/day of ginseng principle fraction 3 was orally administered.  
\*\*\* Volume of ascites evoked by hepatoma was as follows:  
AH 130, 20-50 ml; AH 41C (I), 4-6 ml; AH 41C (II), 20-40 ml.  
+ : Non-significant †† : P < 0.05 ‡‡ : P < 0.02 ‡‡‡ : P < 0.01 ‡‡‡‡ : P < 0.001

**Table 8.** Effect of oral administration of ginseng principle fraction 3 on synthesis of lipid fractions from the liver of normal and tumor-bearing rats (AH 130)

	Number	Total lipids	Free cholesterol	Ester cholesterol	Tri-glyceride	Phospho-lipid
( $\times 10^4$ dpm/100 mg tissue)						
Non-tumor-bearing	8	2.51* + 0.29	1.15 + 0.15	0.033 + 0.004	0.197 + 0.021	0.97 + 0.12
Control diet						
Ginseng diet**	8	4.89 + 0.41	2.03 + 0.27	0.068 + 0.005	0.318 + 0.048	1.56 + 0.23
Tumor-bearing		###	###	###	††	††
Control diet	8	2.20 + 0.19	1.03 + 0.16	0.026 + 0.004	0.158 + 0.021	0.84 + 0.12
Ginseng diet	8	5.57 + 0.62	1.97 + 0.32	0.058 + 0.008	0.295 + 0.034	2.16 + 0.35
		###	††	###	###	###

\* Mean + S.E.

\*\* 1 mg/100 g body weight/day of ginseng principle fraction 3 was orally administered.

†† : P < 0.05

### : P < 0.02

### P : < 0.01

### : P < 0.001

**Table 9.** Effect of oral administration of ginseng principle fraction 3 on incorporation of 1-[ $^{14}$ C]acetate into lipids in adipose tissue from normal and tumor-bearing rats (AH 130)

	Number	Total lipids	Fatty acids
( $\times 10^5$ dpm/100 mg tissue)			
Non-tumor-bearing			
Control diet	8	1.21 + 0.14	0.53 + 0.07*
Ginseng diet**	8	4.64 + 0.62	1.89 + 0.36
Tumor-bearing		###	###
a) Ascites 3-6 ml			
Control diet	8	3.85 + 0.50	2.42 + 0.33
Ginseng diet	8	8.02 + 1.31	4.91 + 0.77
b) Ascites 20-30 ml		###	###
Control diet	8	0.30 + 0.04	0.29 + 0.04
Ginseng diet	8	0.83 + 0.14	0.63 + 0.09
		###	###

\* Mean + S.E.

\*\* 1 mg/100g body weight/day of ginseng principle fraction 3 was orally administered.

### : P < 0.01

### : P < 0.001

**Table 10.** Effect of single administration of ginseng powder on plasma hormonal levels in man

	before	30	60	90	120	150 min
Glucose	100	94	88	91	89	86
Immuno-reactive insulin	100	99	99	94	97	92
Glucagon	100	92	100	96	100	
Cortisol						
Normals	100	120	160	139	112	109
Diabetics	100	88	75	85	80	97
ACTH	100	105	112	106	97	
GH	100		97	83		
Prolactin	100		79	83		
Adrenaline						
Increasing case	100	150	142	293	190	
Decreasing case	100	40	38	27	38	
Noradrenaline	100	83	93	79	95	
Gastrin	100	119	143	123	100	

\* Ginseng powder: 4.5-6 g p.o.

**Table 11.** Effect of ginseng powder on plasma hormones, glucose, lipids and lipid peroxide, in man  
Ginseng powder: 4.5g/day  $\times$  7 days, p.o.

	before	one week later
Glucose	100 + 3*	85 + 3****
IRI	100 + 6	93 + 5**
Cortisol	100 + 12	113 + 12**
Gastrin	100 + 6	128 + 9****
Total cholesterol (TC)	100 + 5	101 + 3**
Over 220 mg/dl	100 + 2	96 + 2**
HDL-Cholesterol	100 + 4	107 + 5****
TC: Over 220 mg/dl	100 + 5	109 + 6***
TC-HDL-C/HDL-C	100 + 5	95 + 6**
TC: Over 220 mg/dl	100 + 7	89 + 6***
Triglyceride (TG)	100 + 18	86 + 14**
TG: Over 130 mg/dl	100 + 5	71 + 2***
Lipid peroxide	100 + 5	103 + 5**

\* Mean + S.E. \*\*N.S. (Non-significant) \*\*\*P < 0.05  
\*\*\*\* P < 0.01 \*\*\*\*\*P < 0.001

Plasma cortisol was enhanced in the normals, while it may be decline in the diabetics. ACTH was increased. As to plasma adrenaline there were two types, the increasing type and the decreasing type. Noradrenaline was slightly decreased. Gastrin was increased especially in patients with relatively high basal levels. TSH, FSH, LH, GH, prolactin, T<sub>3</sub>, T<sub>4</sub> and aldosterone remained unchanged. One week administration of ginseng powder decreased plasma glucose. No significant changes were observed in plasma IRI or cortisol (Table 11). Plasma gastrin was constantly increased. As to plasma lipids, plasma HDL-cholesterol was elevated and atherogenic index was declined. Triglyceride was much decreased.

These data might offer some evidences that ginseng exerted stimulatory effect on pituitary-adrenal axis and also the stimulatory effect in gastric function as well as antiatherogenic effect.

Long-term studies have been performed in the diabetic patients in several hospitals and universities in Japan. The data will be published collectively. Thank you very much for your attention.

**Jin:** Much of the data you presented here seems to be published before in other journals. Is it true or not?

**Yamamoto:** Some of the data was already published but the effect of ginseng in man and especially on HDL cholesterol and lipid is quite new.

## References

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