

# LONG TERM GINSENG EFFECTS ON HYPERLIPIDEMIA IN MAN WITH FURTHER STUDY OF ITS ACTIONS ON ATHEROGENESIS AND FATTY LIVER IN RATS

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## ABSTRACT

In the previous symposium, authors reported about anti-atherogenic action of *Panax ginseng*, saying that red-ginseng powder increased serum HDL-cholesterol, decreased total cholesterol, TG, NEFA, in addition, decreased platelet adhesiveness.

Later, Toyama group including me. reported that ginsenosides esp. Rb<sub>2</sub> enhanced HDL and decreased LDL. Also Matsuyama group and Kinki Univ. group reported that ginsenosides Rg<sub>1</sub>, Rb<sub>2</sub>, etc. inhibited platelet aggregation.

This paper will be divided into two parts:  
Experimental and clinical  
Experimental study;

Using a highcholesterol-cholic acid-fed rats, effects of red ginseng extract and several ginsenosides on serum apoprotein-lipoproteins in relation to prostaglandins.

Rats received 2% cholesterol 1 – 1% cholic acid diet, ginseng extract or ginsenosides 2.5mg/100g/day for 9 days.

Red ginseng extract, ginsenosides Rb<sub>2</sub>, Rc, Rb<sub>1</sub>, and Rg<sub>1</sub>, esp. Rb<sub>2</sub>, increased HDL, apo-AI, Aii and PGI<sub>2</sub>, while they decreased LDL, apo-B and TXA<sub>2</sub>.

### Clinical study:

Effect of red ginseng powder on hyperlipi-

demia was observed.

Long term administration of red ginseng powder manufactured by Office of Monopoly, Republic of Korea and offered by Japan-Korea Korean Ginseng Co., Kobe, at the dose of 2.7g/day, was performed in patients with hyperlipidemia up to 4 years.

The significant increase in serum HDL-cholesterol and also the significant decrease in total cholesterol, atherogenic index, TG, NEFA and lipoperoxide was observed with 3-48 month administration of red ginseng.

### Conclusions:

Red ginseng and ginsenosides improved hyperlipidemia in rats and in man, with the improvement of blood apoproteins, lipoproteins and prostaglandins in experimental hyperlipidemic animals.

## INTRODUCTION

We have been studied the biochemical actions of red ginseng and ginseng principles since 16 years. A part of our data have already presented at the first and the third International Ginseng Symposium about stimulating action of ginseng on bone marrow and testes, along with anti-

atherogenic effect of ginseng.

In this symposium we would like to present the further study of improving action of red ginseng and ginseng principles on experimental hyperlipidemia, specially related to lipoproteins, apoproteins and prostaglandins, together with longterm clinical study of the improving effect of red ginseng on hyperlipidemia.

### Materials and methods

As to experimental study, albino rats of Wistar strain, 8 weeks old were used and hyperlipidemic rats were obtained by feeding 2% cholesterol and 1% cholic acid-containing synthetic diet.

### Results and discussion

Pathogenesis of atherosclerosis which is the most closed associated type with lipid metabolism among three arteriosclerosis. Low density lipoprotein, that is, LDL, rich in cholesterol ester, intruded into affected arterial wall, where acidic cholesterol-esterase splits cholesterol-ester and free cholesterol is subjected to trapping by high density lipoprotein in serum, which transports cholesterol for further degradation to the liver.

Besides, in the case of hyperlipidemia, platelet aggregation is increased, which in turn stimulates blood coagulation on the surface of arterial intima. This favors cholesterol deposit in the arterial wall.

At the last symposium, we showed the improving effect of red ginseng powder on serum lipids in the high cholesterol diet-fed rats. Serum total cholesterol was reduced, while HDL-cholesterol was elevated, so atherogenic index was much declined. Triglyceride (TG) and non-esterified fatty acids (NEFA) were also decreased.<sup>1,2,3)</sup>

Also we showed the improving effect of red ginseng powder on platelet adhesiveness of the high cholesterol diet-fed rats at the last symposium.

Later, Drs. Mitsuma, Yokozawa and Oura of Toyama together with me,<sup>4)</sup> reported the improving effect of various ginsenosides, especially Rb<sub>2</sub> on serum lipoproteins, that is, HDL, elevated and LDL, reduced.

In this paper, we would like to present some data, including those of apoproteins in hyperlipidemic rats.

Table 1 shows the effect of oral administration of water extract of red ginseng corresponding to 100mg of red ginseng per 100g body weight

Table 1. Effect of red ginseng extract and ginsenosides on serum lipids of high cholesterol diet-fed rats.

	Total Cholesterol (TC)	HDL-cholesterol (HDL.C) mg/dl	TC-HDL.C HDL.C	TG (mg/dl)	NEFA (uEq/1)
Normal Diet	(6) 69 ± 2*	47 ± 1	0.5 ± 0.1	81 ± 4	138 ± 14
High Cholesterol diet					
Saline	(6) 181 ± 8	66 ± 2	1.8 ± 0.2	101 ± 6	205 ± 11
Ginsenoside Rb <sub>1</sub>	(5) 142 ± 13	69 ± 2	1.2 ± 0.1	80 ± 6	168 ± 4
Rb <sub>2</sub>	(5) 110 ± 4	81 ± 2	0.4 ± 0.1	66 ± 3	137 ± 15
Rc	(5) 119 ± 5	73 ± 1	0.6 ± 0.1	88 ± 7	168 ± 8
Rg <sub>1</sub>	(5) 171 ± 7	67 ± 4 <sup>+</sup>	1.6 ± 0.2	77 ± 5	158 ± 9
Red Ginseng water extract	(5) 154 ± 9	74 ± 3	0.9 ± 0.1	84 ± 5	168 ± 6

\* Mean ± S.E.

+ : N.S.

per day, together with effect of ginsenosides, 2.5 mg/100g body weight per day, on serum lipid fractions.

As reported before, serum total cholesterol and TG was decreased and HDL-cholesterol was increased by red ginseng powder and ginsenosides, Rb<sub>2</sub>, Rc, Rg<sub>1</sub>, Rb<sub>1</sub>, especially Rb<sub>2</sub>. This data indicates the favorable effect on anti-atherogenesis.

Table 2 shows the effect of red ginseng extract and ginsenosides.

HDL was elevated and LDL was reduced, as reported Toyama group together with me, by ginsenosides and red ginseng extract.

Lipoproteins were consisted of apoproteins and lipids. Recently metabolism of lipoproteins and apoproteins in becoming clearer.

The effect of ginseng on apoproteins is shown in Table 3. Apo-B which is rich in LDL was reduced by red ginseng extract and ginsenosides, while apo-AI and apo-AII which are rich in HDL were elevated by them.

Table 2. Effect of red ginseng extract and ginsenosides on serum lipoproteins of high cholesterol diet-fed rats

	VLDL	LDL	HDL	$\frac{\text{VLDL+LDL}}{\text{HDL}}$
Normal Diet	(6) 24 ± 5	80 ± 26	237 ± 21	0.44
High Cholesterol Diet				
Saline	(6) 127 ± 9	298 ± 18	114 ± 8	3.73
Ginsenoside Rb <sub>1</sub>	(5) 94 ± 14	236 ± 9	156 ± 10	2.12
Rb <sub>2</sub>	(5) 70 ± 4	196 ± 7	232 ± 17	1.15
Rc	(5) 74 ± 7	210 ± 10	196 ± 16	1.45
Rg <sub>1</sub>	(5) 130 ± 11 <sup>#</sup>	220 ± 9	216 ± 22	1.62
Red Ginseng Water Extract	(5) 83 ± 11	261 ± 17	178 ± 14	1.93

\* Mean ± S.E.

#: N.S.

Table 3. Effect of red ginseng extract and ginsenosides on serum apoproteins of high-cholesterol diet fed rats

	Apo-B	Apo-AI	Apo-AII (mg/dl)	$\frac{\text{B}}{\text{AI+AII}}$
Normal Diet	28 ± 5*	59 ± 7	12 ± 2	0.39
High Cholesterol Diet				
Saline	45 ± 2	148 ± 4	19 ± 5	0.27
Ginsenoside Rb <sub>1</sub>	28 ± 4	162 ± 12	26 ± 1	0.15
Rb <sub>2</sub>	22 ± 1	216 ± 12	31 ± 1	0.09
Rc	27 ± 4	174 ± 9	30 ± 2	0.13
Rg <sub>1</sub>	27 ± 3	257 ± 25	19 ± 1 <sup>+</sup>	0.10
Red Ginseng Water Extract	39 ± 3	194 ± 5	21 ± 1 <sup>+</sup>	0.18

\* Mean ± S.E.

+ N.S.

As written before, platelet aggregation is responsible for atherogenesis. Platelet aggregation is accelerated by thromboxane A<sub>2</sub> (TXA<sub>2</sub>), one of prostaglandins, while it is inhibited by prostacyclin (PGI<sub>2</sub>), also one of prostaglandins.

Plasma Thromboxane B<sub>2</sub>, a stable form derived from thromboxane A<sub>2</sub>, was reduced by red ginseng extract and ginsenosides, especially Rb<sub>2</sub>. (Table 4). On the contrary, plasma 6-keto-prostaglandin F<sub>1</sub>α, a stable form derived from prostacyclin was enhanced by them. This fact may favor anti-atherogenesis.

Dr. Kaneko group and Dr. Kubo group reported ginsenoside Rg<sub>1</sub> inhibited platelet aggregation.

The fatty liver induced by high cholesterol feeding was also improved by red ginseng and ginsenosides, as shown in table 5. Hepatic cholesterol and TG were decreased and phospholipid was increased. Histological findings supported these biochemical improvement.

As to extensive clinical study of ginseng effects have already started from those on unsettled complaints, performed by Prof. Arichi group and Dr. Kumashima group, as reported at the last symposium. Recently, we also added some data on this point in patients with diabetes melli-

tus or arteriosclerosis.

As we already presented here as the experimental study, ginseng might have the improving action of hyperlipidemia even in man.

We started the long term clinical study of clinical effect of red ginseng powder in patients with hyperlipidemia in 1979 in Nissei Hospital and the 2nd Department of Internal Medicine, Chiba University.

Sixty seven patients with hyperlipidemia mainly complicated with diabetes mellitus, received Korean Red Ginseng Powder manufactured by Office of Monopoly, Republic of Korea, offered by Japan Korea Red Ginseng Co., Kobe, Japan, at the dose of 2.7g per day up to 2 years or more.

Table 6 shows sequential serum lipid levels of Red Ginseng Powder administered group. Statistically significant improvements were observed in serum lipids in patients with hyperlipidemia, that is, serum HDL-cholesterol was significantly increased after 1 month while significant decreases were observed in serum total cholesterol, atherogenic index, also TG, NEFA and even lipoperoxide after 3 months, up to 24 months.

Figure 1 shows the relationship between

Table 4. Effect of red ginseng extract and ginsenosides on plasma prostaglandins of high-cholesterol diet fed rats

	Thromboxane B <sub>2</sub> (TXB <sub>2</sub> )	6-keto-prostaglandin F <sub>1</sub> α (6-keto-PG) (pg/ml)	$\frac{\text{TXB}_2}{\text{6-keto-PG}}$
Normal	(4) 186 ± 18*	(5) 233 ± 10	0.8
High Cholesterol Diet			
Saline	(6) 714 ± 78	(6) 112 ± 13	6.4
Ginsenoside Rb <sub>1</sub>	(4) 197 ± 20	(5) 89 ± 11	2.2
Rb <sub>2</sub>	(4) 262 ± 14	(4) 233 ± 19	1.1
Rc	(5) 465 ± 78	(4) 320 ± 98	1.5
Rg <sub>1</sub>	(4) 297 ± 27	(4) 229 ± 74	1.3
Red Ginseng Water Extract	(4) 307 ± 33	(4) 190 ± 28	1.6

\* Mean ± S.E.

Table 5. Effect of red ginseng extract and ginsenosides on hepatic lipids of high-cholesterol diet fed rats

	Total Cholesterol	TG	Phospholipid (c/p) (mg/g)	FFA (uEq/g)
Normal diet	(5) 2.6 ± 0.03*	5.9 ± 0.1	5.7 ± 0.1 (0.5)	16 ± 0.1
High Cholesterol Diet				
Saline	(6) 8.4 ± 0.3	8.6 ± 0.2	3.0 ± 0.1 (2.8)	46 ± 0.1
Ginsenoside Rb <sub>1</sub>	(5) 7.2 ± 0.1	7.5 ± 0.1	3.8 ± 0.1 (1.9)	38 ± 1
Rb <sub>2</sub>	(5) 6.5 ± 0.2	5.9 ± 0.2	4.0 ± 0.2 (1.6)	29 ± 1
Rc	(5) 6.8 ± 0.1	6.0 ± 0.1	3.4 ± 0.1 (2.0)	32 ± 1
Rg <sub>1</sub>	(5) 6.7 ± 0.1	6.9 ± 0.3	3.8 ± 0.1 (1.8)	42 ± 1
Red Ginseng Water Extract	(5) 6.7 ± 0.1	6.8 ± 0.1	3.7 ± 0.1 (1.8)	26 ± 1

\* Mean ± S.E.

Table 6. Effect of Korean Red Ginseng Powder on Serum lipidi levels in patients with hyperlipidemia (67 cases)

	Before	1	3	6	12	18	24months
Total Cholesterol (mg/dl)	256 ± 8 <sup>o</sup> (67)	240 ± 9 (39)*****	227 ± 9 (46)*****	212 ± 7 (36)*****	211 ± 11 (17)***	241 ± 25 (7)***	215 ± 9 (5)*****
HDL-cholesterol (mg/dl)	42 ± 2 (56)	44 ± 3 (24)*****	43 ± 2 (35)*****	48 ± 2 (30)*****	47 ± 3 (13)*****	42 ± 3 (5)*****	50 ± 5 (4)**
Atherogenic Index	5.7 ± 0.4 (56)	5.0 ± 0.5 (22)*****	4.7 ± 0.5 (31)*****	3.6 ± 0.3 (30)*****	3.9 ± 0.3 (13)***	5.2 ± 1.1 (5)*	3.6 ± 0.6 (3)**
Triglyceride (mg/dl)	160 ± 9 (67)	134 ± 9 (40)*****	141 ± 11 (47)*****	119 ± 7 (37)*****	116 ± 10 (17)*****	129 ± 18 (6)*****	133 ± 18 (5)**
NEFA (uEq/l)	685 ± 45 (67)	593 ± 81 (37)*****	514 ± 42 (46)*****	440 ± 38 (36)*****	423 ± 40 (16)*****	481 ± 52 (6)***	434 ± 86 (4)****
Liperoxide (nmol/ml)	4.4 ± 0.2 (50)	3.8 ± 0.2 (20)****	4.1 ± 0.2 (26)****	3.6 ± 0.2 (23)*****	4.0 ± 0.2 (9)**	3.7 ± 0.5 (3)*	3.8 ± 0.4 (5)****

Korean Red Ginseng Powder: 2.7g/day, p.o., <sup>o</sup>Mean ± S.E. \*N.S., \*\*P 0.05, \*\*\*p 0.02, \*\*\*\*p 0.01, \*\*\*\*\*p 0.001

ginseng effects on serum HDL-cholesterol and the initial levels of them before treatment. The lower initial levels, the higher their increasing ratios.

Figure 2 shows also the relationship between ginseng effect on serum total cholesterol and the initial levels of them before treatment. This time, the higher initial levels, the lower their decreasing ratios.

The same tendency is also observed in serum TG.

At the last symposium Dr. Keun et al. re-

ported that alcoholinduced hyperuricemia was improved by ginseng in rats. Our clinical study also indicates hyperuricemia-improving action of Red Ginseng Powder in patients with hyperuricemia. (Table 7).

The relationship between serum HDL-cholesterol and TG, showed a reciprocal change. Also as to the relationship between serum HDL-cholesterol and uric acid, the similar tendency was observed.

Table 8 shows the relationship between

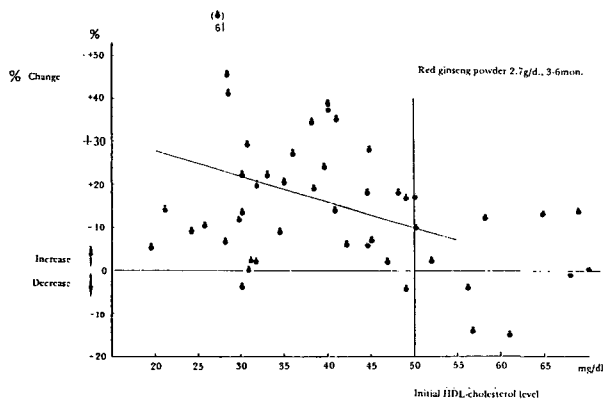


Fig. 1. Relationship between ginseng effect on serum HDL-cholesterol and initial level.

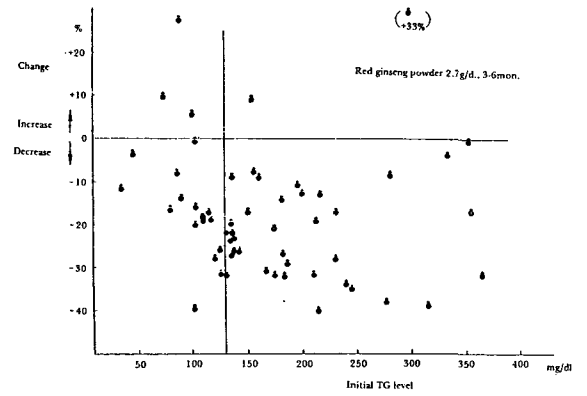


Fig. 3. Relationship between ginseng effect on serum TG and initial level.

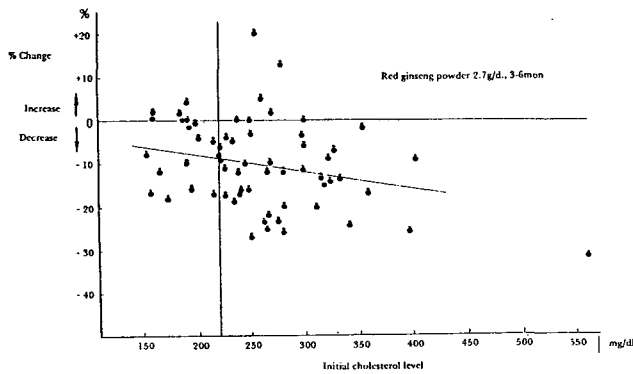


Fig. 2. Relationship between ginseng effect on serum cholesterol and initial level.

Table 7. Effect of Korean red ginseng administration on plasma uric acid levels in patients with hyperuricemia<sup>+</sup>

	Cases	Uric acid	
Before	(9)	9.0 ± 0.5*	
1 month	(8)	7.5 ± 0.4	P < 0.01
3 month	(6)	6.7 ± 0.4	P < 0.001
6 month	(2)	6.9 ± 0.1	P < 0.05
12 month	(1)	6.0 ± 0	N.S.

\* Mean ± S.E. + UA > 7.0mg/dl

Table 8. Relationship between % change in serum lipids by ginseng and obesity degree

		Degree of obesity (initial) (%)					
		< -20	-20~10	-10~+10	+10~+20	+20~+40	+40<
Percentage of Change (%)	Cholesterol	12 ± 4*	7 ± 5	10 ± 2	13 ± 3	10 ± 3	0 ± 2
	↓ (no.)	4	3	20	13	14	2
Percentage of Change (%)	HDL-cholesterol	16 ± 9	30 ± 10	14 ± 3	5 ± 6	16 ± 4	10 ± 5
	↑ (No.)	3	4	19	7	13	2
Percentage of Change (%)	Triglyceride	32 ± 2	20 ± 3	21 ± 2	15 ± 4	13 ± 5	1 ± 33
	↓ (No.)	5	5	21	11	13	2

\* Mean ± S.E.: Mean values of serum lipids 3 and 6 mon. after red ginseng administration (2.7g/d).

obesity degree and the ginseng effect. In non-obese patients, ginseng effect is clearer, as compared with obese patients. It is reaffirmed that diet therapy including caloric restriction, should

be preceded by drug therapy.

Conclusions it is conceivable that *panax ginseng* and ginsenosides might have anti-atherogenic effects in rats and in man.

**I.P. Lee:** I'd like to ask you about the lipid changes such as triglycerides, fatty acids, especially the cholesterol level change. And is the extent of that change statistically significant?

How would you relate those changes to any clinical improvement among these patients? Can you make any relationship between the biochemical change and clinical improvements?

**Yamamoto:** We checked the lipid level for the first time. Next time we are going to check the clinical effect of ginseng by employing double blind trials and also the long-term effect on the incidence of coronary diseases.

**Chong:** Were those patients in your clinical study – were they put on the concurrent medical treatment throughout the period of study or not in your two groups of patients?

The second question is that I think it would probably be more interesting if you had stopped the ginseng after the period of treatment to see whether the cholesterol level actually increased.

**Yamamoto:** Like other anti-lipidemic drugs, when we stopped the medication the lipid level returned to the previous levels.

## 사람의 과지혈증과 동맥경화 및 흰쥐 지방간에 미치는 인삼의 장기복용 효과 연구

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제 3 차 인삼심포지움에서 저자는 홍삼분말의 투여로 혈청의 HDL-콜레스테롤이 증가되며 총 콜레스테롤, 중성지방, 유리지방산이 감소하며, 특히 혈소판 응집현상이 감소되어 인삼이 항동맥경화능을 갖는다고 발표하였다.

이후에 본인을 포함한 토야마대학 연구팀은 진세노사이드 특히 Rb<sub>2</sub>가 HDL 콜레스테롤 양을 증진시

키며 LDL을 감소시킨다고 보고하였다. 또한 마쓰야마 연구진과 킨키대학 연구팀은 진세노사이드 Rg<sub>1</sub>, Rb<sub>2</sub> 등이 혈소판 응집을 억제시킨다고 발표하였다. 본 논문은 크게 두 부분, 즉 실험동물 연구와 임상연구로 나뉘어져 있다.

### 실험동물연구

고함량의 콜레스테롤-콜린산을 함유한 사료로 사육한 흰쥐를 실험 동물로 사용하여, 인삼추출물과 몇 가지 진세노사이드 등이 혈청 아포단백질, 지방 단백질 및 프로스타글란딘에 미치는 영향을 연구하였다. 2% 콜레스테롤, 1% 콜린산을 함유한 사료로 사육한 흰쥐에게 매일 체중 100g당 2.5mg의 인삼추출물 또는 진세노사이드를 9일간 투여하였다. 홍삼추출물, 진세노사이드 Rb<sub>2</sub>, Rc, Rb, 그리고 Rg<sub>1</sub> 특히 Rb<sub>2</sub>는 HDL 콜레스테롤, apo-A I, A II 그리고 PGI<sub>2</sub>의 양을 증가시켰으나, LDL, apo-B, TXA<sub>2</sub>의 양은 감소시켰다.

### - 임상연구 -

홍삼분말이 과지혈증에 미치는 영향을 연구하였다. 대한민국 전매청에서 생산된 홍삼분말을 Japan-Korea Korean Ginseng Co. 코베에서 공급받아 1일 2.7g의 용량으로 과지혈증 환자에게 4년까지 장기투여하였다. 홍삼을 3~48개월 투여하게 되면, HDL 콜레스테롤 양이 현저히 증가하였으며, 총 콜레스테롤 양, 동맥경화지표, 중성지방, 유리지방산, 과산화지방은 현저히 감소하였다.

### - 결 론 -

홍삼과 진세노사이드는 사람과 흰쥐에 있어 과지혈증을 호전시켰다. 실험적으로 과지혈증을 유발시킨 흰쥐에서, 혈중 아포단백질, 지방단백질 및 프로스타글란딘 상호성을 개선시켰다.

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