Effect of *Panax ginseng* on Hyperlipidemia and Diabetes Mellitus

Masahiro Yamamoto

Dept. of Internal Medicine, Nissei Hospital Osaka, Japan

We have been studied about biochemical and pharmacological actions of *Panax ginseng* principles, especially of ginsensides, which Profs Tanaka and Shibata group determined.

The first slide shows the various actions of ginseng which we have been engaged in. Stimulatory action on DNA, RNA, protein and lipid synthesis as well as cell division in bone marrow and testes; lipid metabolism improving actions which I intend to talk mainly today(Table 1).

Next slide(Fig.1) shows the pathogenesis of atherosclerosis briefly. Cholesterol in LDL(low density lipoprotein) which comes into arterial wall evokes atherosclerosis. On the other hand, cholesterol which formed from cholesterol-ester in the arterial wall, is trapped as the form of HDL(high density lipoprotein)-cholesterol in the blood. So increased HDL-cholesterol and decreased LDL-cholesterol favor anti-atherogenesis. Besides inhibition of platelet aggregation also favar anti-atherogenesis.

Effects of various ginsenosides, together with hot water extract of red ginseng on experimental hyperlipidemia by 2% cholesterol-1% cholic acid diet feeding, were observed, as we already reported[1]. At first the effects on serum lipids are shown. Total cholesterol, and triglyceride

Table 1. *Metabolic and endocrine actions of ginseng saponins.* **(Yamamoto, M.** *et al.* 1969~)

Bone marrow
Synthesis of DNA, RNA, protein, lipid↑
Cell division↑
Testicle
Synthesis of DNA, protein↑
Tumor
Synthesis of DNA, protein, lipid~
Tumor bearing animal: Lipogenesis↑
Adipose tissue
Lipogenesis↑, Lipolysis↓
Hyperlipidemia(Cholesterol↓, TG↓, LDL↓, HDL↑,
Apo-B↓, Apo-AI-AII↑ (animal, man)
Platelet adhesiveness↓
Fatty liver (Cholesterol↓, TG↓, PL↑, NEFA↓, LPO↓)
Cerebral circulation (man)
Blood hormone levels (man)
Glucose↘, IRI~, glucagon~, GH~,
adrenalin↑↓, noradrenalin↑↓, gastrin↑~,
cortisol↑ (↘ in DM), ACTH↑

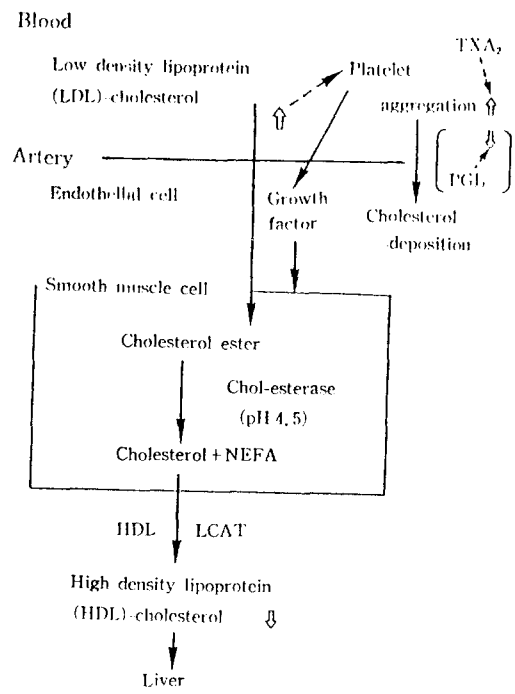

Fig.1. *Pathogenesis of atherosclerosis.*

Table 2. *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 μEq/l
Normal diet	(6) 69±2*	47±1	0.5± 0.1	81±4	138±14
High cholesterol diet					
Saline	(5) 181±8	66±2	1.8±0.2	101±6	205±11
Ginsenoside Rb_1	(5) 142±13[2)]	69±2†	1.2±0.1[3)]	80±6[1)]	168±4[1)]
Rb_2	(5) 110±4[3)]	81±2[3)]	0.4±0.1[3)]	66±3[2)]	137±15[2)]
Rc	(5) 119±5[3)]	73±1[2)]	0.6±0.1[3)]	88±7†	168±8[1)]
Rg_1	(5) 171±7†	67±4†	1.6±0.2†	77±5[1)]	158±9[1)]
Red ginseng water extract	(5) 154±9[1)]	74±3[2)]	0.9±0.1[3)]	84±5[1)]	168±6[1)]

*Mean±S.E. †: N.S. 1) P<0.05 2) P<0.01 3) P<0.001

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

	VLDL	LDL	HDL mg/dl	VLDL+LDL / 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_1	(5) 94±14†	236±9[1)]	156±10[2)]	2.12
Rb_2	(5) 70±4[3)]	196±7[3)]	232±17[1)]	1.15
Rc	(5) 74±7[2)]	210±10[3)]	196±16[1)]	1.45
Rg_1	(5) 130±11†	220±9[3)]	216±22[1)]	1.62
Red ginseng Water extract	(5) 83±11[1)]	261±17†	178±14[2)]	1.93

*Mean±S.E. †: N.S. 1) P<0.05 2) P<0.01 3) P<0.001

decreased, while HDL-cholesterol increased with ginsenosides administration. Atherogenic index was reduced(Table 2).

The 4th slide(Table 3) shows the effect on serum lipoproteins. VLDL(very low density lipoprotein) and LDL are reduced, which HDL increased.

The effect on serum apolipoproteins is shown on the 5th slide(Table 4). Apo-B, rich in LDL, decreased and apo AI-AII, rich in HDL, increased. Next, I will talk about plasma prostanoids in association with platelet aggregation. Mechanism of serum cholesterol lowering was reported before[2)].

Thromboxane A_2 exerts platelet aggregation and prostacyclin inhibits it, as you know. Plasma level of thromboxane A_2 metabolite was decreased and prostacyclin metabolite, 6-keto-$PGF_{1\alpha}$ was increased by ginsenoside administration(Table 5).

All these data favor anti-atherogenesis.

In a high cholesterol diet fed rats, we observe fatty liver with increased cholesterol and triglyceride and decreased phospholipid. With ginsenoside administration, these changes were improved. Lipoperoxide was also much

Table 4. *Effect of red ginseng extract and ginsenosides on serum apoproteins of high cholesterol diet-fed rats.*

	Apo-B	Apo-AI	Apo-AII	B
			mg/dl	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_1	28±4[2)]	162±12†	26±1†	0.15
Rb_2	22±1[3)]	216±12[3)]	31±1[1)]	0.09
Rc	27±4[2)]	174±9[1)]	30±2[1)]	0.13
Rg_1	27±3[3)]	257±25[3)]	19±1†	0.10
Red ginseng Water extract	39±3†	194±5[3)]	21±1†	0.18

*Mean±S.E. †: N.S. 1) $P<0.05$ 2) $P<0.01$ 3) $P<0.001$

Table 5. *Effect of red ginseng extract and ginsenosides on plasma prostaglandins of high cholesterol diet-fed rats.*

	Thromboxane B_2 (TX B_2)	6-Keto-prostaglandin F_1 (6-Keto-PG)	TX B_2/6-Keto-PG
		pg/ml	
Normal diet	(4) 186±18*	(5) 233±10	0.8
High cholesterol diet			
Saline	(6) 714±78	(6) 112±13	6.4
Ginsenoside Rb_1	(4) 197±20[3)]	(5) 89±11	2.2
Rb_2	(4) 262±14[3)]	(4) 233±19[3)]	1.1
Rc	(5) 465±78[1)]	(4) 320±98[3)]	1.5
Rg_1	(4) 297±27[3)]	(4) 229±74[3)]	1.3
Red ginseng Water extract	(4) 307±33[3)]	(4) 190±28[1)]	1.6

*Mean±S.E. 1) $P<0.05$ 2) $P<0.01$ 3) $P<0.001$

decreased(Table 6).

We will proceed to clinical data. As we reported before, long term administration of Korean Red Ginseng Powder, produced by Office of Monopoly, Republic of Korea, 2.7g/day was performed in 67 patients with hyperlipidemia up to 2 years[3)].

Serum total cholesterol, triglyceride, nonesterified fatty acids and lipoperoxide, while HDL-cholesterol was increased(Table 7).

According to hyperlipidemia classification by WHO, patients were divided into types. Abnormal changes in serum lipids were improved in either of type IIa, IIb or IV(Table 8).

I will show an example of type IIa hyperlipidemic patient treated with Red Ginseng Powder.

Serum lipid, lipoprotein and apoprotein levels were improved(Table 9).

This is another example of heterozygote hyperlipidemia type IIa, Red Ginseng was used together with cholestyramine, because of drug allergy to almost all types of antihyperlipidemic drugs. Addition of Red Ginseng, either of lipids, lipo- or apolipoproteins was improved(Table 10).

Table 6. *Effect of red ginseng extract and ginsenosides on hepatic lipids of high cholesterol diet-fed rats.*

	Total cholesterol	TG mg/g	Phospholipid [C/P]	FFA μEq/g	Lipoperoxide nmol/g
Normal diet	(5) 2.6±0.03*	5.9±0.1	5.7±0.1 [0.5]	16±0.1	2.7±0.2
High cholesterol diet					
Saline	(6) 8.4±0.3	8.6±0.2	3.0±0.1 [2.8]	46±0.1	6.0±0.1
Ginsenoside Rb_1	(5) 7.2±0.1[2)]	7.5±0.1[3)]	3.8±0.1[3)][1.9]	38±1[3)]	2.5±0.1[3)]
Rb_2	(5) 6.5±0.2[3)]	5.9±0.2[3)]	4.0±0.2[3)][1.6]	29±1[3)]	1.9±0.1[3)]
Rc	(5) 6.8±0.1[3)]	6.0±0.1[3)]	3.4±0.1[1)][2.0]	32±1[3)]	3.3±0.1[3)]
Rg_1	(5) 6.7±0.1[3)]	6.9±0.2[3)]	3.8±0.1[3)][1.8]	42±1[1)]	3.1±0.1[3)]
Red ginseng Water extract	(5) 6.7±0.1[3)]	6.8±0.1[3)]	3.7±0.1[3)][1.8]	26±1[3)]	2.2±0.1[3)]

*Mean±S.E. 1) $P<0.05$ 2) $P<0.01$ 3) $P<0.001$

Table 7. *Effect of red ginseng powder on serum lipid levels in patients with hyperlipidemia(67 cases).*

	Before	1	3	6	12	18	24 Months
Total chol.	256±8°	240±9	227±9	212±7	211±11	241±25	215±9
mg/dl	(67)	(39)****	(46)****	(36)****	(17)***	(7)***	(5)***
HDL-chol.	42±2	44±3	43±2	48±2	47±3	42±3	50±5
mg/dl	(56)	(24)*****	(35)*****	(30)*****	(13)*****	(5)*****	(4)**
Atherogenic	5.7±0.4	5.0±0.5	4.7±0.5	3.6±0.3	3.9±0.3	5.2±1.1	3.6±0.6
index	(56)	(22)*****	(31)*****	(30)*****	(13)***	(5)**	(3)**
Tiglyceride	160±9	134±9	141±11	119±7	116±10	129±18	143±18
mg/dl	(67)	(40)*****	(47)*****	(37)*****	(17)*****	(6)***	(5)**
NEFA	685±45	593±81	514±42	440±38	423±40	481±52	434±86
μEq/l	(67)	(37)*****	(46)*****	(36)*****	(16)*****	(6)***	(4)***
Lipoperoxide	4.4±0.2	3.8±0.2	4.1±0.2	3.6±0.2	4.0±0.2	3.7±0.5	3.8±0.4
nmol/ml	(50)	(20)$P<0.1$	(26)****	(23)*****	(9)**	(3)*	(5)$P<0.1$

Korean red ginseng powder: 2.7 g/day p.o. ◦Mean±S.E. * N.S. ** $P<0.05$ '*** $P<0.02$ **** $P<0.01$ ***** $P<0.001$

Table 8. *Relationship between improving ratios in serum lipids and types of hyperlipoproteinemia.*

Type	Improving ratio in Total chol.	TG	HDL-chol.
IIa	77.3	39.1	63.2%
IIb	84.2	89.5	93.8
IV	50.0	83.3	75.0

The 12th slide shows a tentative summary of Red Ginseng effects on serum lipid, lipoprotein and apoprotein levels. Improvements in apo B, CII-CIII and AI-AII as well as LDL, VLDL and HDL were observed(Table 11).

As we reported before, serum uric acid level was also observed with long term administration of Red Ginseng Powder in hyperuricemic patients(Table 12).

Now, we proceed to another topic.

This slide is borrowed from Prof. Oura, Toyama Med. Pharm. Univ. Ginsenoside Rb_2 strongly reduced serum glucose level in streptozotocin-treated diabetic rats(not shown).

Table 9. *T.R. female 64 y.o.a., Coronary insufficiency with hyperlipidemia type IIa BH 148 BW 50*

	Before	2w	4w
Tchol.	282⇧	257↓	247↓
TG	78	64	90
HDL-chol.	57	58	53
NEFA	310	393	337
Chylom.	0	0	0
VLDL	35	25	31
LDL	994 ⇗	889↓	698↓
HDL	574	460↘	445↘
LDL/HDL	1.7	1.8↓	1.6
Apo-B	163	108	134↓
AI	130	146	137
AII	—	—	—
CII	16.3	5.0	5.3↓
CIII	—	—	—
E	—	—	—
B/AI	1.3	0.7	1.0
LPO	7.1⇧	6.8↓	5.3↓

No such data can not be obtained in clinical diabetes mellitus, as to serum sugar and insulin levels.

However, general complaints especially in relation to peripheral circulatory disturbance as well as fatique or malaise, tended to be improved(Table 13).

Among diabetic complications, neuropathy was improved to some extent, when used after several months of diabetes control by diet and drugs(Table 14).

The last topic is on effect of ginsenosides on liver cell proliferation in cell culture medium.

Bovine serum and epidermal growth factor(EGF) seems to be necessary for the action of ginsenoside(Table 15).

The 17th slide(Table 16) shows the stimulatory effect of some of ginsenosides on liver cell proliferation in the presence of EGF and bovine serum. By the way, we have reported stimulatory effects of ginsenosides on DNA, protein and lipid synthesis in bone marrow and testes[4].

The last 18th slide shows albumin formation in cultured liver cells. Some ginsenosides were also effective(Table 17).

Ginsenoside effects on carbon tetrachloride induced hepatic damage were reported in this country. I myself reported red ginseng and ginsenoside effect on α-naphtyl isothiocyanate(ANIT)-induced hepatobiliary

Table 10. *Changes of blood lipids, lipoproteins and apolipoproteins.*

		Normal value	0 VI'81	3m. IX'81	6m. XII'81	1y. VI'82	2y. VI'83	3y. VI'84	4y. VI'85	5y. VI'86
T-ch	mg/dl	116-241	546	468	408	380	376	349	383	365
HDL-ch		30- 74	34	36	39	43	49	47	50	55
TG		43-173	78	71	85	52	59	60	49	72
Atherogenic index		-3.5	15.1	12.0	9.5	7.8	6.7	6.4	6.7	5.6
"β-lipoprotein"		1.0-2.2	6.6	4.9	5.4	-	-	-	-	-
HDL	mg/dl	125-425	(575)						643	706
LDL		-630	(1625)						1162	1277
VLDL		-200	(195)						82	72
Chylomicron		0	0						0	0
Apo-AI	mg/dl	117-151	-						101	81
Apo-AII		27- 39	-						25	17
Apo-B		35-155	-						280	223

Table 11. *Effect of oral administration of Korean red ginseng powder on lipids, lipoproteins and apoproteins in the blood from patients with hyperlipidemia*

	Before	1	3	6	9	12	15 Months
Lipids:							
Total cholesterol	100*	91	94	88	110	105	98%
HDL-cholesterol	100	97	109	106	134	112	112
TG	100	92	78	71	46	71	59
Lipoperoxide	100	100	66	89	55	73	55
Lipoproteins:							
VLDL	100	40	36	42	54	60	52
LDL	100	88	101	80	87	94	97
HDL	100	119	113	109		105	
Apoproteins:							
Apo-B	100	94	84	76	81	90	96
Apo-AI	100	126	116	112	106	117	
Apo-CII	100	42	50	50		47	

*Percentage of the initial level
Red ginseng powder: manifactured by Office of Monopoly, Republic of Korea

Table 12. *Effect of red ginseng powder on serum uric acid level.*

	Before	1	3	6	12	18	24 Months
Hyperuricemia	9.0±0.5°	7.5±0.4	6.7±0.4	6.9±0.1	6.0±0		
UA:>7 mg/dl	(9)	(8)****	(6)*****	(2)**	(1)*		
All cases	5.7±0.3	5.6±0.3	6.7±0.7	5.1±0.3	4.6±0.3	5.3±0.6	
	(50)	(43)*	(4)*	(18)*	(10)*	(3)*	

Korean red ginseng powder : 2.7 g/day p.o. ∘ Mean±S.E. * N.S. ** $P<0.05$ **** $P<0.01$ ***** $P<0.001$ Serum uric acid

Table 13. *Percentage of improved cases of indefinite complaints with Korean Red Ginseng Powder in patients with diabetes.*

	Placebo (%)		Ginseng* (%)			
	1 mon	2 mon	1 mon	2 mon	3 mon	6 mon
General condition	4.3	(0)	27.3 ($X^2_0=5.2$, $p<0.05$)**	41.2	72.7	71.4
Fatigue	4.2	(0)	30.4 ($X^2_0=6.4$, $p<0.02$)	17.6	38.5	37.5
Appetite	4.3	(0)	22.7 ($X^2_0=3.5, 0.05$ $p<1.0$)	35.3	25.0	75.0
Insomnia	10.0	(0)	21.1 (N.S.)	33.3	50.0	37.5
Cold on extremities	13.6	(0)	47.6 ($X^2_0=6.1$, $p<0.02$)	50.0	40.0	50.0
Stool	0	(0)	22.2 (N.S.)	33.3	33.3	12.5
Weakness	5.3	(0)	33.3 ($X^2_0=5.1$, $p<0.05$)	28.6	36.4	50.0
Face color	0	(0)	18.8 (N.S.)	7.7	25.0	16.7
Palpitation	0	(0)	29.4 ($X^2_0=7.6$, $p<0.01$)	30.8	33.3	50.0
Short breathlessness	13.3	(0)	33.3 ($X^2_0=1.8$, N.S.)	41.7	40.0	57.1
Cold on lumbar area	6.7	(0)	7.1 (N.S.)	18.2	12.5	33.3
Lumbar pain	11.1	(50)	17.6 (N.S.)	15.4	45.5	75.0

Ear ringing	10.0	(0)	50.0 (X^2_0=3.8, 0.05 p<0.1)	71.4	85.7	80.0
Dizziness	9.5	(50)	20.0 (N.S.)	35.3	54.5	33.3
Postural dizziness	6.7	(0)	35.7 (X^2_0=4.2, p<0.05)	50.0	44.4	28.6
Sweating	0	—	0 (N.S.)	13.3	9.1	0
Shoulder tension	12.5	(33)	21.7 (N.S.)	28.6	50.0	75.0
Muscle & joint stiffness	4.5	(100)	19.0 (N.S.)	31.3	23.0	37.5
Headache	6.3	(0)	20.0 (N.S.)	30.0	44.4	42.9
Stomachache	8.3	(0)	25.0 (N.S.)	54.5	66.7	50.0
Abdominal fullness	15.8	(0)	16.7 (N.S.)	13.3	20.0	50.0

* Ginseng: Korean Red Ginseng Powder 2.7 g/day
** Statistical significance: Placebo 1 mon. vs. Ginseng 1 mon
(%): Two few cases

Table 14. *Effect of administration of red ginseng powder in patients with diabetic neuropathy.*

	Ratio of improvement (%) 6 Months
Pain on extremities	15/44 (34.1%)
Numbness on extremities	28/44 (63.6%)
Abnormalities of tendon reflexes	7/28 (25.0%)
Vibration sensation (mean of 4 limbs)	28 cases
Before 6.4±0.4*	
After 7.9±0.5** sec.	

*Mean±S.E. **p<0.05
Diet+insulin or S.U. at least for 6 months before ginseng administration

Table 15. *Effect of ginsenoside on liver cell proliferation in relation to EGF and calf serum*

Calf serum (-):	
No addition	1.0
EGF, 1 ng/m*l*	1.2
Ginsenoside Rb_2, 5 ug/m*l*	1.3
EGF+Rb_2	1.4
Calf serum, 10% (+):	
No addition	1.1
EGF, 1 ng/m*l*	1.4
Ginsenoside Rb_2, 5 ug/m*l*	1.3
EGF+Rb_2	1.5

37°C, 96 hours, viable cells, n=4

Table 16. *Effect of ginsenosides on proliferation of cultured liver cells*

Ginsenosides	Cell count (X10^5/well)
No addition	1.1±0.1*
Ro	1.3±0.2 N.S.
Rb_1	1.6±0.2 p<0.05
Rb_2	1.7±0.2 p<0.05
Rc	1.6±0.2 p<0.05
Rd	1.3±0.2 N.S.
Re	1.4±0.2 N.S.
Rg_1	1.6±0.2 p<0.05

37°C, 96 hours, viable cells
*Mean±S.E., n=6
Newborn calf serum, 10%
EGF, 1 ng/m*l*

Table 17. *Effect of ginsenosides on albumin production in cultured liver cells.*

Ginsenosides	Albumin produced
No addition	100±7*%
Ro	138±10 p<0.05
Rb_1	130±15 N.S.
Rb_2	140±12 p<0.05
Rc	156±14 p<0.05
Rd	106±7 N.S.
Re	108±11 N.S.
Rg_1	114±6 N.S.

37°, 48 hours
*Mean±S.E., n=4

damage[5].

If there is restoration of damaged liver cells in hepatic damage clinically, these effects might be beneficial to treatment of some of hepatic diseases.

In summary, we presented here about some clinical effects on hyperlipidemia and diabetes, together with their experimental basis including effects on hepatic damage.

References

1. Yamamoto, M. *et al.: J. Med. Pharm. Soc.* for WAKAN-YAKU **2:** 377-385, 1985.
2. Yamamoto, M. *et al.: Amer. J. Chin. Med.* **11:** 80-97, 1983.
3. Yamamoto, M. *et al.: Proc. Jap. Soc.* Clin. Biochem. **19:** 46-48, 1982.
4. Yamamoto, M. *et al.: Arzneimittel-forschung.* **28:** 2238-2241, 1978.
5. Yamamoto, M. *et al.: J. Med. Pharm. Soc.* for WAKAN-YAKU **2:** 386-397, 1985.