PHARMACOLOGICAL STUDIES ON GINSENG

Keijiro TAKAGI
Faculty of Pharmaceutical Sciences, University of Tokyo, Japan

Ginseng has been used from several thousand years ago in China and now it is used in Korea, Japan and Europe as folk medicine. Its chemical and pharmacological studies have been reported by many investigators of many countries. But its pharmacological properties have not been completely investigated and their research remains on the step of the crude extract. Dr. Shibata in our Faculty separated ginseng saponins, determined their chemical structures, and supplied us crude saponin fractions and individual saponins. So our pharmacological studies started on several saponin-containing fractions.

At the beginning of pharmacological studies on ginseng we were interested in central nervous system activities and behavioral effects of ginseng fractions, and then the investigation was extended to general pharmacological assay upon various ginseng fractions isolated according to a systematic separation.

As general pharmaoclogical blind screening we adopted next 5 items:

(1) neuropharmacological observation on mice,
(2) tests on blood pressure and respiration of the rat,
(3) tests on isolated guinea pig ileum,
(4) effects on hexabarbital hypnosis of the mouse,
(5) effect on writhing response induced by 0.7% acetic acid in the mouse.

Generally about 70 pharmacological actions can be estimated by these methods on the drug tested.

Fig. 1 shows separating system of various saponins and other fractions including water-soluble and ether-soluble substances. Numbers cited in each fraction indicate pharmacological actions found respectively. That is,

(1) slight CNS stimulant action,
(2) CNS depressant action,
(3) tranquillizing action, or sedative action,
(4) cholinergic action,
(5) histamine-like action,
(6) blood pressure fall,
(7) blood pressure elevation,

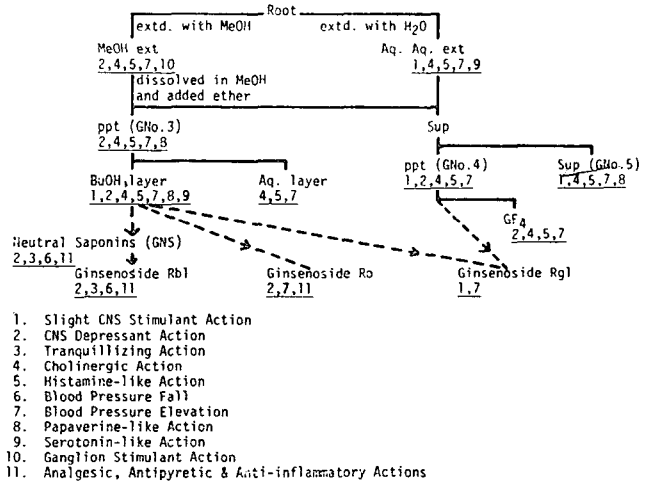

Fig. 1 Separation of Panax Ginseng Root Extracts and Pharmacological Activities Estimated

Table 1. Estimated Actions of Panax Ginseng Root by Blind Screening

Estimated Actions	References
1. Slight CNS-Stimulant Action	Petkov, W.; 1968, Brekhman, I. I. & Dardymov, I. V.; 1969 Kim, E. C. et al.; 1971
2. CNS-Depressant Action	Kim, E. C. et al; 1971
3. Tranquillizing Action	Kim, E. C. et al.; 1971
4. Cholinergic Action	Petkov, W.; 1968, Wood, W. B. et a l.; 1964
5. Histamine-like Action	Lee, W. C. et al.; 1960, Choi, K. D. et al.; 1963
6. Blood Pressure Fall	Wood, W. B. et al.; 1964, Kitagawa, H. et al.; 1963
7. Blood Pressure Elevation	Sakai, Y.; 1915
8. Papaverine-like Action	Petkov, W.; 1959
9. Serotonin-like Action	Hwang, W. T. & Park, D. I.; 1960
10. Ganglion Stimulant Action	
11. Analgestic, Antipyretic & Anti-inflammatory Actions	
12. No Antihistamine-like Action	Petkov, W.; 1959 (Kitagawa, H. et al.; 1963 ,Antihistamine-like Action)

(8) papaverine-like action,
(9) serotonin-like action,
(10) ganglion-stimulant action,
(11) analgesic and anti-inflammatory actions.

CNS stimulating action was found in G No4, ginsenoside Rgl and lipid soluble fraction G No5. CNS depressant action, on the other hand, was observed in G No3 GNS and ginsenoside RB1.

Cholinergic and histamine-like actions, shown as temporary blood pressure fall, were blocked by atropine and diphenhydramine respectively. They were transferred mainly to water solution. After the blockade now blood pressure elevation is disclosed.

Ginsenoside Rb1 exhibited rather prolonged blood pressure fall which can not be blocked by the above blockers, (Takagi, K. et al., 1972).

The pharmacological activities predicted in the general pharmacological assay as above have been already reported by many investigators as show in Table 1, where crude extracts were used exclusively.

In the next step we report CNS depressant activities of various fractions:,

(1) Potentiating activity of hexobarbital hypnosis 70 mg/kg injected intraperitoneally to the mouse,
(2) spontaneous movement decrease of the mouse in activity wheel,
(3) depression of CR or UR of the rat in pole-climbing test,
(4) decrease of motor coordination of the mouse in rotating rod test (Fig. 2).

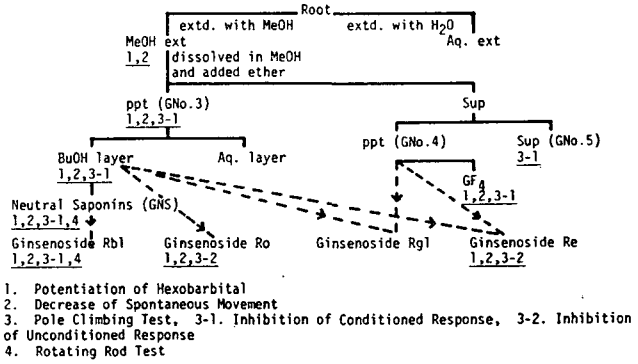

Fig. 2 Separation of Panax Ginseng Root Extracts and CNS Depressant Activities of The Fractions Obtained

CNS depressant action was found in all saponin except ginsenoside Rgl, especially ginsenoside Rb1 which belongs to panaxadiol saponin, has rather remarkable sedative, tranquillizing action. Here we must cite that leaf saponin fraction from ginseng has similar depressant action.

Further studies on CNS action of GNS, GRb1, GF4 and GF-DS-II (total saponin fraction of ginseng leaf), are shown in Table 2. Numerical values in this table are dosages given and asterisk shows significant depressant effect at 5% probability level. Decreases of motor coordination, body tone and grip tone, body temperature lowering, and antipyretic action were found in every fraction listed. Spontaneous movement, which was tested on four methods, was decreased apparently by the fractions tested.

Table 2. Pharmacological Properties of GNS (Neutral Saponins), Ginsenoside Rbl, GF4 & GF-DS-II (Leaves Saponins) (Dose: mg/kg)

Tests	Route	Fractions GNS	Ginsenoside Rbl	GF_4	GF-DS-II
1. Acute Toxicity in Mice	p.o.	>5000	>5000		>5000
	i.p.	545	1208		306
	i.v.	367	492		299
2. Rotating Rod Test in Mice	i.p.	160*	150*	—100*	100*
in Rats	i.p.	150*	90*	30*	60*
3. Sliding Angle Test in Mice	i.p.	400*	600*		400*
4. Spring Balance Test in Mice	i.p.	400*	300*		200*
5. Suspension Test in Rats	i.p.	150*	90*	100*	90*
6. Hypothermia in Mice	i.p.	100*	100*	50*	200*
7. Antipyretic Test in Mice	i.p.	200*	200*		200*
8. Motor Activity Test in Mice					
Hole Cross Test	i.p.	50*	50*	20*	20*
Activity Wheel Test	i.p.	100*	100*		200*
Phtotransister Recorder Test	p.o. (chronic)	100*	100*		100*
Spring Recorder Test	p.o. (chronic)	100*			
9. Climbing Test in Mice	i.p.	50*	20*	100*	25*
10. Potentiation of Hexobarbital in Mice	i.p.	100*	25*	100*	200*
11. Analgesic Test in Mice					
Writhing induced by acetic acid	p.o.	200*	100*	300±	100*
Tail Pressure Test	i.p.	100*	100*		100*
12. Anticonvulsant Test in Mice					
Electroshock	i.p.	200*	800*		400*
Pentylenetetrazol	i.p.	100*	100*		100*
Strychnine	i.p.	100*	100*		100*
13. Fighting Behavior Test in Mice	i.p.	400*	500*		400*
14. Pole Climbing Test in Rats	i.p.				
Delay of Response Latency		10*	10*	10*	3*
Inhibition of Conditioned Response		10*	10*	10*	3*
Inhibition of Unconditioned Response		200*	200*	30*	30*
15. Shuttle Box Test in Rats	i.p.				
Delay of Response Latency		10*	3*	10*	
Inhibition of Conditioned Response		10*	3*	10*	
Inhibition of Unconditioned Response		200*	200*	30*	
16. Y-maze Test in Rats	i.p.				
Delay of Response Latency			10*		
Delay of Running Time			3*		
Error			200±		
Inhibition of Correct Response			10*		
17. Food Consumption Test in Rats	i.p.		30* (Decrease)		

*: Significant at $p = 0.05$, & ±. No Effec

Exploratory movement tested by climbing test was significantly decreased. (Saito, H. et. al., 1973; Na bata, H., et al., 1973; Takagi, K., et al., 1974)

Analgesic action was significant in all fractions except saponin-free GF4. Anti-electroshock and anti-chemoshock effects and inhibition of fighting behavior of mice were also significant. Conditioned avoidance response was remarkablely depressed by all fractions tested.

Performance of earning effect was depressed by ginsenoside Rbl on Y-maze and food consumption was also decreased.

All these effects show that ginsenoside Rbl and similar saponins may have some tranquillizing, anti-anxiety effects.

G No4 and its main saponin, ginsenoside Rgl showed CNS depressant action in higher doses. But in smaller doses as 10 mg/kg shortening of response

Table 3. Pharmacological Properties of GNo. 4, Ginsenoside Rgl & GNo. 5
(Dose: mg/kg)

Tests	Route	Fractions GNo. 4	Ginsenoside Rgl	GNo. 5
1. Acute Toxicity in Mice	p.o.	>5000	>5000	>5000
	i.p.	>2000	1600	>4000
	i.v.		396	
2. Rotating Rod Test in Mice	i.p.	1000*	400*	3000*
in Rats	i.p.	> 200	> 180	> 200
3. Sliding Angle Test in Mice	i.p.	1000*	> 800	3000*
4. Spring Balance Test in Mice	i.p.	1000*	> 800	3000*
5. Suspension Test in Rats	i.p.	> 200	> 180	> 200
6. Hypothermia in Mice	i.p.	500*	1000*	3000*
7. Motor Activity				
Hole Cross Test in Mice	i.p.	100* ↓	1000 ↓ *	2000 ↓ *
Activity Wheel Test in Mice	i.p.		1000 ↓ *	
Phototransister Recorder in Mice	p.o. (Chronic)	10 (*) ↑	10 ↑ (*)	10±
Spring Recorder in Mice	p.o. (Chronic)	10±	10 ↑ (*)	10 ↑ (*)
8. Potentiation of Hexobarbital in Mice	i.p.	200 ↑ *	> 800	> 500
9. Antagonism to Reserpine	i.p.	>400	> 500	>1000
	i.p.	RL: 10 ↑ (*)	RL: 180 ↓ *	RL: 10 ↑ (*)
10. Pole Climbing Test in Rats	i.p.	CR: 100 ↓ *		CR: 100 ↓ *

*: Significant at $p = 0.05$,Student's t-Test, (*): $p = 0.10$, & ± & > : No Effect
↓ : Decrease or Prolongation, & ↑ : Increase or Shortening
CR: Conditioned Response, RL: Response Latency

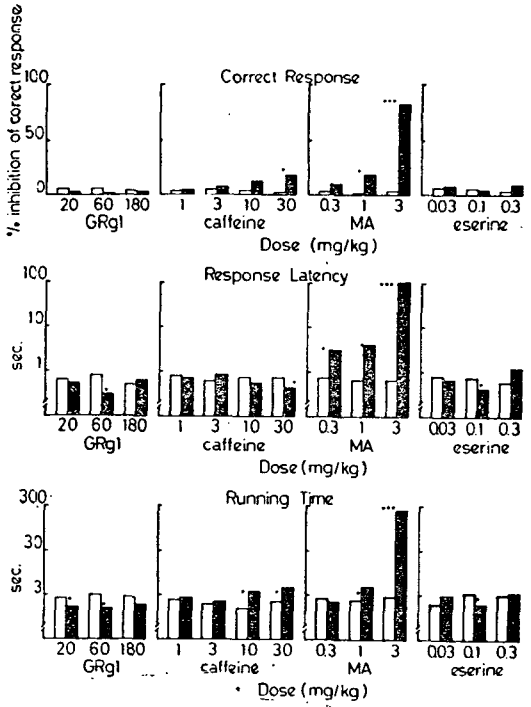

Fig. 3 Effect of Ginsenoside Rgl on Performance of Learning of The Rat in Y-maze

latency was observed in pole climbing test, and increase of motor activity (Table 3).

Further investigation for CNS activation by the ginseng saponin was tried on Y-maze test. At the end of right side path a piece of cheese was placed. By training the rat remembered the right path and run straightly for food (Fig. 3). Influence of ginsenoside Rgl on the rat performance was determined.

Duration from opening of the gate to start of the animal is called as response latency (RL). Correct response means that response latency and running time (RT) are within 2 sec. respectively and that the rat runs straightly to the object.

As shown in Fig. 4 caffeine and methamphetamine inhibited apparently correct response, but ginsenoside Rgl and eserine did not. Response latency was decreased by Rgl, caffeine and eserine but methamphetamine increased it significantly. Running time was shortened sinificantly by Rgl and partly by eserine. On the other hand caffeine and methamphetamine prolonged it significantly. Accordingly ginsenoside Rgl possesses somewhat different CNS stimulating action from caffeine and MA, which is called as CNS activating action.

The existence of cholinergic, histamine-like, papaverine-like activities and effects on blood pressure were further investigated on the way of frac-

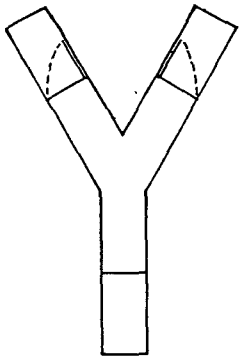

Fig. 4 Schematic Presentation of Y-maze

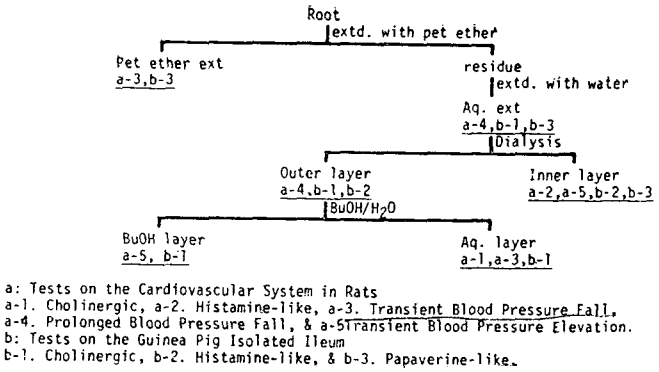

Fig. 5 Separation of Korean Ginseng Extract and Distribution Some Pharmacologic Activities

Table 4. Effect of Panax Ginseng Root (Korea)

Tests	per ether ext	Aq. ext	Inner layer	Outer layer	Aq. layer	BuOH layer
a. Cardiovascular System in Rats						
Cholinergic					10 mg/kg	
Histamine-like			3 mg/kg*			
BP Fall (Transient)	1 mg/kg*				10 mg/kg*	
BP Fall (Prolonged)		1 mg/kg*		3 mg/kg*		
BP Elevation			1 mg/kg*			1 mg/kg*
b. Guinea Pig Isolated Ileum						
Cholinergic		10^{-7} g/ml*		10^{-6} g/ml*	10^{-6} g/ml*	10^{-4} g/ml*
Histamine-like			10^{-6} g/ml*	10^{-5} g/ml*		
Papaverine-like	10^{-4} g/ml*	10^{-4} g/ml*	10^{-4} g/m*l			

*: Significant at $p = 0.05$, Student's t-Test

Table 5. Pharmacological Actions of Panax Ginseng Root not Presumed by Blind Screening

Actions	References
Antifatigue Action	Sterner, W.: 1969, Brekhman, I. I. et al.: 1969, Kitagawa, et al.: 1963, Takagi, K. et al.: 1974 & Saito, H. et al. :1974
Stomachic Action	"YAKUCHOU" (ca 1750 AD, Japan)
CNS-Activating Action	"EMPEROR SHEN NUNG" (ca 2700 BC, China)
Antidiabetic Action	Brekhman, I. I. et al.: 1969, Kimura, M. et al. :1973
Hematogenic Action	Brebhman, I. I. et al.: 1965, Petkov, W.: 1968, Ooura, H. et al.: 1971

Table 6. Antifatigue Activity

Enforced Exercise:	A 4 hr Oscillation Movement
Methods Employed after a 4 hr Exercise	
1. Rectal Temperature (RT) Test:	Rectal Temperature
2. Rotating Rod (RR) Test:	Motor Coordination
3. Sliding Angle (SA) Test:	Motor Coordination and Body Tone
4. Spring Balance (SB) Test:	Grip Tone
5. Hole Cross (HC) Test:	Spontaneous Movement
6. Exploratory Movement (EM) Test:	Exploratory and Spontaneous Movements

Table 7. Effect of Panax Ginseng Root on Exhaustion in Mice

Recovery from Exhaustion									
Extracts		Aq. ext			Ginsenoside Rgl			GNo. 5	
Tests	Dose mg/kg, i.p.	50	10	200	12.5	50	200	100	200	400
1. RT Test		−		+		(+)	+	+	+	
2. RR Test		(+)			(+)	(+)	(+)		(+)	+
3. SA Test			(−)			(+)				−
4. SB Test				−	+			−	+	
5. HC Test				−	+			−		
6. EM Test: Light → Dark		+	+	+	(+)	(+)	+		+	
Dark→Light (I)			+	(+)		+	+	+		+
Dark → Light (II)						(+)				
Motor Activity			+	(+)		+	+		+	+

+ (Increase), − (Decrease): Significant at p = 0.05, Student's t-Test
Parenthesis indicate such a tendency (p = 0.10)
Drugs were administered just after the 4 hr oscillation. Test 1, 2, 3 & 4 were performed twice: 30 & 120 min after exercise. Test 5 was done for 1 hr, 1 hr after exercise, & test 6 for 30 min, 10 min after exercise

Table 8. Effect of Panax Ginseng Root on Gastrointestinal Systems

Tests	MeOH ext	Aq. ext	BuOH ext	GRo	GRbl	GRgl
1. Water Immersion Stress in Mice (6 hr) i.p.	400 mg/kg ↓ *	400 mg/kg±	100 mg/kg ↓ *	100 mg/kg ↓ **	25 mg(/kg ↓ *	50 mg/kg ↑ ** 200 mg/kg ↓ *
2. Potentiation of Hexobarbital in Mice i.p.	100 mg/kg±	250 mg/kg ↑ (*)	500 mg/kg ↑ (*)	300 mg/kg ↑ **	50 mg/kg ↑ *	400 mg/kg±
3. Gastrointestinal Motility in Mice p.o.	1000 mg/kg±	1000 mg/kg±	1000 gm/kg ↑ *	400 mg/kg±	100 mg/kg ↑ *	400 mg/kg±
4. Pylorus Ligation in Rats (4 hr) i.d.						
Volume	1000 mg/kg ↓ (*)	1000 mg/kg ↓ (*)	1000 mg/kg±	400 mg/kg ↓ ***	400 mg/kg±	400 mg/kg±
Acid Output	1000 mg/kg±	1000 mg/kg±	1000 mg/kg±	400 mg/kg ↓ ***	400 mg/kg±	400 mg/kg±
Pepsin Output	1000 mg/kg±	1000 mg/kg±	1000 mg/kg±	400 mg/kg ↓ ***	400 mg/kg±	400 mg/kg±
5. Guinea Pig Isolated Ileum						
Cholinergic	10^{-6} g/ml*	10^{-8} g/ml*	10^{-7} g/ml*			
Histamine-like	10^{-5} g/ml*	10^{-8} g/ml*	10^{-7} g/ml*			
Papaverine-like	10^{-4} g/ml***		10^{-4} g/ml***			

***: Significant at p = 0.01, Student's t-Test, **: p = 0.02, *: p = 0.05, & (*): p = 0.10
↑ : Increase, ↓ : Decrease & ± No Effect

tionation of Korean ginseng. Anti-peptic ulcer action and effect on small intestinal motility were also tested. Cholinemimetic activity was proved by blood pressure decrease and ileum contraction and their blockade by atropine. The activity was found as water-soluble and dialysable. Blood pressure elevation was observed in undialyzable fraction and in BuOH extract contained saponin. (Fig. 5) Restraint and water immersion stress ulcer of the mouse was not affected by water extract, but after dialysis anti-ulcer activity was found especially in BuOH extract containing saponin.

Table 4 shows effective doses and concentrations in the above mentioned pharmacologic activities.

Further study is in progress in our laboratory in this direction.

Pharmacological actions listed in Table 5 have been mentioned in ancient chinese medicine or found in animal experiments by many authors. First three

of them were tested in our laboratory, of which 2nd and 3rd had been suggested by the previous general, screening.

After various forced works or stress were applied to the mouse for producing fatigued state, oscillation method that the animals were placed on the oscillating plate was selected as the hardest work. After 4 hr oscillation follwing 6 tests were tried to recognize fatigued states (Table 6).

(1) rectal temperature decrease,
(2) decrease of motor coordination on rotating rod,
(3) decrease of motor coordination and body tone by sliding angle test,
(4) lowered grip tone, that is, muscle strength by spring balance test,
(5) decrease of spontaneous movements of the grouped mice in hole cross test,
(6) decreased exploratory movements in exploratory movement box.

Fig. 6 shows an apparatus for exploratory movements used in our laboratory. It consists of a box with 3 compartments. The two outer compartments are transparent and connected to the darkened middle one by round openings respectively. Three kinds of exploratory movements and spontaneous movement are measured.

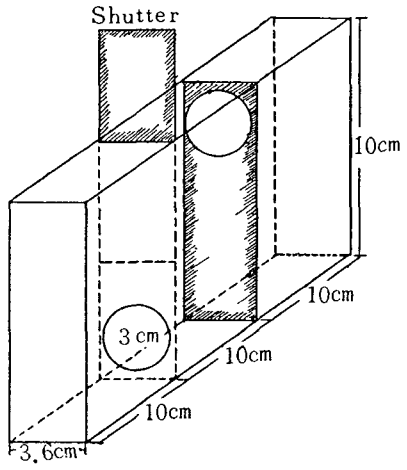

Fig. 6 Schematic Presentation of Exploratory Apparatus

(1) The time it takes the mouse to pass to the middle compartment after the shutter was opened,
(2) The time it takes the animal to climb up to the opposite 2nd hole,
(3) The time to enter the 3rd light compartment,
(4) Frequency that the mouse climbs up to the 2nd hole during 30 min. as index of spontaneous movement.

After 4hr oscillation various ginseng fractions were administered to the animals, and restoration from fatigue was measured in the previous tests (Table 7). (Saito, H. et al., 1974)

Water extract, ginsenoside Rg1 and G No. 5 showed antifatigue activity significantly.

+ and − signs show significant results at 0.05 probability level. Signs in parenthesis indicate such a tendency.

Ginsenoside Rg1 even at 12.5 mg/kg showed significant antifatigue action.

Effects of various fractions on gastrointestinal tract were tested (Table 8). Restraint and water immersion stress ulcer of the mouse was inhibited by 25 mg/kg of ginsenoside Rb1 and aggravated by 50 mg/kg of ginsenoside Rg1. The former is sedative and the latter is week CNS stimulant. Ginsenoside Rb1 promoted intestinal motility.

Inhibition of gastric secretion was recognised in MeOH or water extracts but week.

Before the start of experiments on learning absense of disturbing effect of ginsenoside Rg1 on motor coordination and food consumption was confirmed in doses from 10 to 180 mg/kg. In pole climing test 10 to 30 mg/kg of ginsenoside Rg1 administered for 10 days promoted acquisition of discriminationre sponse between 2 different sounds (Table 9).

In Y maze test ginsenoside Rg1 20 to 60 mg/kg increased discrimination performance as shown already Fig. 4. It also promoted acquisition of discrimination response and acquisition of reversal learning, where the target that is, cheese was transferred to another side from, right to left.

Acquisition of discrimination learning in pole climbing test was shown in Fig. 7. Groups treated with ginsenoside Rg1 acquired rapidly discrimination, so correct response was increased. Open circles show ginsenoside Rg1 treated groups. They are higher than the control group.

In Fig. 8 results of reversal learning are shown. Ginsenoside Rg1 and eserine accerelate the acquisi-

Table 9. Effect of Ginsenoside Rgl on Behaviour in Rats

Tests	Route	Ginsenoside Rgl
1. Pole Climbing Test		
CR-Performance	i.p.	20–60 mg/kg ±, 180 mg/kg ↓ (*)
CR-Acquisition (3 Days)	i.p.	10–100 mg/kg±
CR-Extinction (3 Days)	i.p.	30 & 120 mg/kg ±, 60 mg/kg ↓ (*)
DR-Performance (Sound-Sound)	i.p.	20–180 mg/kg±
DR-Acquisition (Sound-Sound, 10 Days)	i.p.	10 & 30 mg/kg ↑ *
CR(Sound) → DR (Sound)-Acquisition (1 Week)	i.p.	10 & 50 mg/kg ↑ (*)
2. Y-Maze Test		
DR-Performance (Right-Left)	i.p.	20 mg/kg RT ↑ *, 60 mg/kg RT ↑ * & RL ↑ *
DR-Acquisition (Right-Left, 10 Days)	i.p.	10 & 50 mg/kg ↑ *
Reversal Learning (Right-Left, 3 Days)	i.p.	10 & 50 mg/kg ↑ *
3. Rotating Rod Test	i.p.	10–180 mg/kg±
4. Food Consumption Test	i.p.	10–180 mg/kg±

*: Significant at p = 0.05, Student's t-Test, (*): p = 0.10, & ±: No Effect
↓ : Decrease or Prolongation & ↑ : Facilitation or Shortening
CR: Conditioned Response, DR: Discriminable Response, RL: Response Latency & RT: Running Time

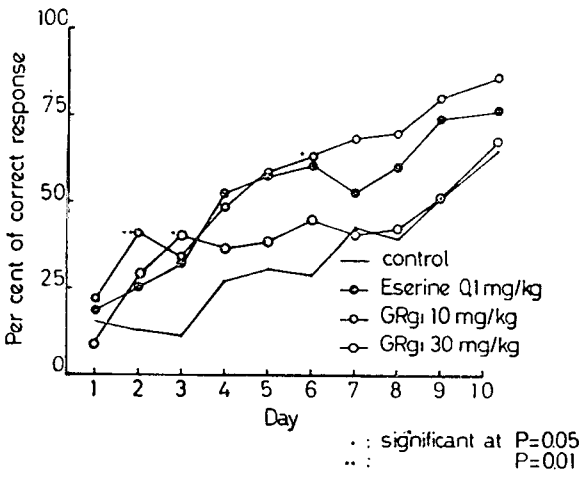

Fig. 7 Effect of Ginsenoside Rgl on Acquisition of Discrimination Learning in Pole Climbing Test

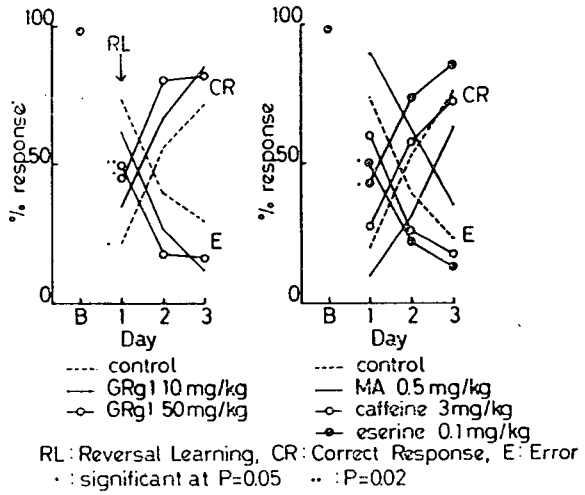

Fig. 8 Effect of Ginsenoside Rgl on Reversal Learning in Y-maze

tion of reversal learning. After the rats had been trained to get the target in the right side, the target was transferred to the another left side and the trial began again. Correct response in the reversal learning of the animals treated with ginsenoside Rgl was higher than the control.

As a summary ginsenoside Rb1, of which aglycone is protopanaxadiol exerts CNS depressant action. In water soluble and lipid soluble fractions other depressant substances may exist.

Ginsenoside Rgl and lipid soluble G No. 5 fraction exihibited CNS-stimulating activity. The former promoting, for example, discrimination learning in Y maze is called CNS activating substance by us, and the latter is rather similar activity to amphetamine, but very weak. Anti-fatigue activity is found in ginsenoside Rgl and partly in G No. 5.

Cholinergic substance was found in water soluble substance of small molecular weight. Histamine-like substance is larger molecular weight and water soluble.

Protective effect on stress ulcer of the mouse was exhibited by saponin fractions. Spontaneous movements of small intestine was promoted by ginseno-

Table 10. Pharmacological Active Substances of Panax Ginseng Root

Actions		Ingredients
CNS-Depressant Action	3	S (Protopanaxadiol & Oleanolic Acid Glycosides), W & L
Tranquillizing Action	2	Ginsenoside Rbl & W
CNS-Stimulant Action	2	Ginsenoside Rgl & L
Cholinergic Action	1	W (Outer: Dialysis)
Histamine-like Action	1	W (Inner: Dialysis)
Blood Pressure Elevation	2	S (Oleanolic Acid & Protopanaxatriol Glycosides) & W (Inner: Dialysis)
Blood Pressure Fall	2	S (Protopanaxadiol Glycoside) & L
Papaverine-like Action	2	L & W (Outer: Dialysis)
Antifatigue Action	2	Ginsenoside Rgl & L
Effects on Gastrointestinal Systems	2	L & S (Oleanolic Acid Glycoside)

S: Saponins, W: Water Soluble Substances (Not Saponins) & L: Lipid Soluble Substances

side *R*b1 (Table 10).

We consider that multiple pharmacodynamic activities of ginseng are originated from various ingredients. Some ingredients have antagonistic action each other, for example, CNS-stimulating and depressant, or hypertensive and hypotensive.

How these antagonistic activities present themselves can not be decided now.

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