The Effect of Ginseng Saponins and Phenolic Acids on the Biosynthesis of Prostaglandins

C.W. Park and S.H. Lee
College of Medicine, Seoul National University, Seoul 110-460, Korea

Korean ginseng, *Panax ginseng* C.A. Meyer, has been known for its miraculous effects in folk medicine more than 2,000 years. During the past 50-60 years, more scientific concepts and methodology have been applied for the investigation of the pharmacological effects of ginseng. The reported pharmacological action of *Panax ginseng* can be summarized as follow;

1) Stimulative & sedative effects on the CNS
2) Antistress effects
3) Hypotensive effects
4) Antifatigue effects
5) Effects on high blood sugar
6) Effects on high cholesterol level
7) Anticancer effects
8) Stimulatory effects on the GI motility & tone
9) Beneficial effects on the disorders related to anemia
10) Antiinflammatory effects
11) Adaptogenic effect

Although a considerable amount of evidence has been accumulated on the pharmacological effect of *Panax ginseng*, such a multifarious pharmacological action makes it passible to suggest some humoral factor through which the effects of ginseng might be mediated. The prostaglandins could be considered to be one of such humoral factor. Therefore, the effects of ginseng saponin on the *in vitro* biosynthesis of prostaglandins was examined to identify the role of ginseng components on the regulation of arachidonic acid metabolism.

First, production of individual prostaglandins from the exogenous [^{3}H]AA by various enzyme RKM, BAM, & HPH was determined. While PGE_2 & $PGF_{2\alpha}$ production were highest by RKM compared with BAM or HPH, TxB_2 production was highest by HPH, & P.C. was by BAM. From this result, different tissues were chosen to evaluate the production of PGs, such as RKM for PGE_2 & $PGF_{2\alpha}$ BAM for P.C., & HPH for TxB_2.

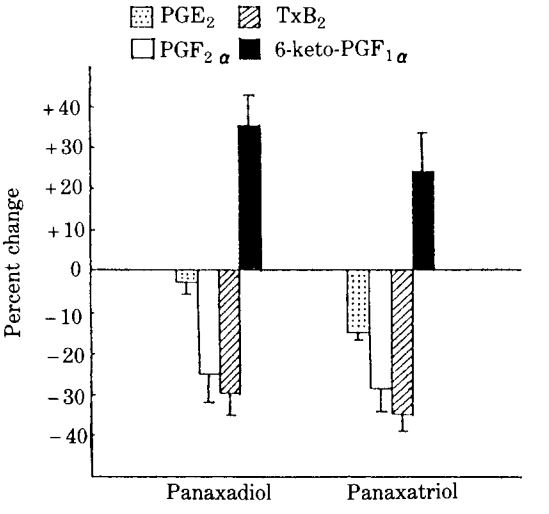

Fig. 1. Effects of panaxadiol and panaxatriol (5×10^{-4} g/m*l*) on the formation of PGs.

The amounts of total cyclooxygenase products produced by various enzyme source did not show any significant changes in the presence of ginseng saponins.

But each divergent prostaglandin productions are influenced by ginseng saponins. Both panaxadiol or panaxatriol increased the 6 keto-$PGF_{1\alpha}$ production and suppressed the $PGF_{2\alpha}$ production but PGE_2 production was not influenced significantly.

Ginsenoside Rb_2 also increased the production of 6K-$PGF_{1\alpha}$ and decreased the production of TxB_2 dose dependently but the productions of PGE_2 and $PGF_{2\alpha}$ were not significantly influenced by

Table 1. Effects of ginseng saponin on the formation on total PGs by cyclooxygenase

Compound	Level of total PGs (%, M±S.D.)*		
	RKM	BAM	HPH
Control	18.7±2.1	16.7±1.8	23.2±2.5
panaxadiol 500 g/ml	15.7±4.2	20.2±2.4	22.4±2.7
Panaxatriol 500 g/ml	15.6±4.0	17.8±2.2	22.6±3.0
G-Rb_2 500 g/ml	16.9±2.0	17.4±2.0	19.4±2.1
G-Rc 500 g/ml	19.1±1.7	20.4±2.6	17.1±2.5
G-Re 500 g/ml	20.7±2.2	18.9±1.6	21.6±2.2

* Data were presented as percent of products formed from (^{3}H)-AA.

ginsenoside Rb_2 in concentration of 10 to 1000 ug/ml. This results are consistent with the results of panaxadiol & panaxatriol as whom on previous slide.

In the presence of ginsenoside Rc, the production of 6keto-$PGF_{1\alpha}$ was increased but that of PGE_2, $PGF_{2\alpha}$ were decreased dose-dependently. The results of PGE_2 is somewhat different from the result of panaxadiol, panaxatriol, & G-Rb_2. However, the stimulation of P.C. production & the inhibition of TxB_2 production were consistent.

The effect of ginsenoside Re on divergent prostaglandin production was quite similar to that of ginsenoside Rb_2, the production of 6k-$PGF_{1\alpha}$ was increased and that of TxB_2 was decreased dose-dependently but the productions of PGE_2 and $PGF_{2\alpha}$ were not affected.

To determine effect ginseng saponin on cyclooxygenase, the effect of indomethacin, C.O. inhibitor, or epinephrine, C.O. stimulator was examined using R.K.M.

Comparing with the effect of indomethacin or epinephrine, the stimulatory or inhibitory effect of ginseng saponins on the production of PGE_2 was not significant. While a significant inhibitory effect on the $PGF_{2\alpha}$ was observed with the treatment of panaxadiol, panaxatriol, & G-Rb_2. From this result we could conclude the inhibitory effect of $PGF_{2\alpha}$ production was partly, if not mainly, due to the inhibition of C.O. Further investigation of the mechanism

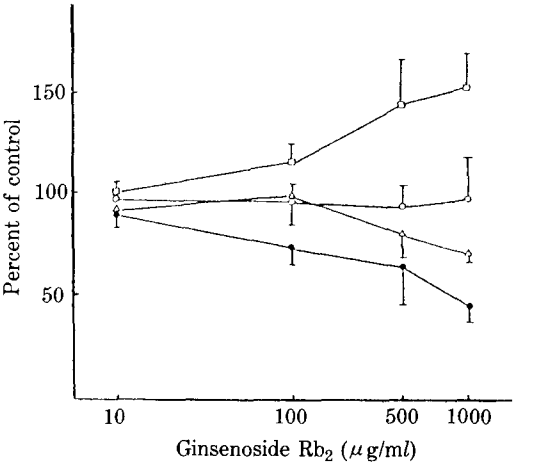

Fig. 2. Effects on G-Rb_2 on the formation PGs (n=5). (○) PGE_2; (△) $PGF_{2\alpha}$; (●) TxB_2; (□) 6-keto-$PGF_{1\alpha}$

Table 2. Effects of some ginsenosides on human platelet aggregation induced by ADP and sodium arachidonate

Compound	Percent light transmission (M±S.D.)[a]	
	ADP (10 M)	AA-Na (1 mM)
Control	77.5±2.9	74.0±5.0
Imidazole 5 mM	64.6±4.8	15.6±3.1*
Indomethacin 40 M	51.3±4.1*	26.3±5.2*
Panaxadiol 0.5 mg/ml	74.4±3.5	17.5±3.3*
Panaxatriol 0.5 mg/ml	78.8±5.9	21.3±6.8*
G-Rb_1 0.5 mg/ml	71.3±4.7	71.9±5.9
G-Rb_2 0.5 mg/ml	74.4±5.8	18.1±5.1*
G-Rc 0.5 mg/ml	78.1±4.5	16.3±4.8*
G-Re 0.5 mg/ml	74.3±3.6	36.3±9.7*
G-Rg_1 0.5 mg/ml	70.0±5.7	14.4±4.5*

[a] n=5
*; $P<0.01$.

of the inhibition of Tx synthesis was performed using imidazole, inhibitor of Tx synthetase.

The effect of ginseng saponins in a concentration of 500 ug/ml on the formation of TxB_2 was compared with that of imidazole in using HPH as enzyme source. In general, ginseng saponins suppress the production of TxB_2 and the potency of ginsenoside Rb in a concentration of 500 ug/ml was

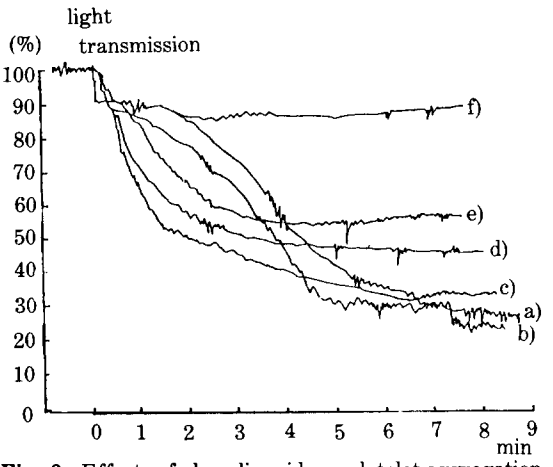

Fig. 3. Effects of phenolic acids on platelet aggregation induced by U46619 (0.5 M, a)
b) Salicylic acid c) Maltol d) Vanillic acid
e) trans-p-Coumaric aicd, 1 mM, and f) Imidazole, 5 mM.

Table 3. Effects of phenolic acids on the formation of total PGs

Compound	Level of total PGs (%[a]/protein 5 mg, M±S.D.)		
	RKM	BAM	HPH
Control	18.7±1.6	16.7±1.8	42.1±3.2
Maltol 1 mM	18.9±2.0	17.9±1.6	37.2±3.1
p-Coumaric acid 1 mM	14.4±1.5*	7.2±1.9*	18.8±1.6*
Salicylic acid 1 mM	13.1±1.2*	13.9±2.3	38.1±2.8

[a] Values were presented as percentages of total cyclooxygenase products converted fro, (^{3}H)-AA.
*; $P<0.01$

equivalent with that of imidazole in a concentrations of 2 mM.

And ginseng saponins seems to potentiate the effect of imidazole additively. When HPH was treated with ginsenosides and imidazole together, the inhibitory effect of TxB_2 production was potentiated. Therefore, the inhibitory effect of the TxB_2 production by ginseng saponins may be mainly due to the inhibition of the Tx synthetase.

The production of 6K-$PGF_{1\alpha}$ in the BAM was inhibited by tranylcypromine dose dependently and the inhibitory effect of tranylcypromine on production of 6K-$PGF_{1\alpha}$ was nearly completely reversed by ginsenosides.

The biological significance of the effect of ginseng saponins, on production of TxB_2 was evaluated by the effect of ginsenoside on human platelet aggregation. Sodium arachidonate induced platelet aggretation was significantly inhibited by all the ginseng saponins tested except ginsenoside Rb1 but ADP induced platelet aggregation was not affected. While indomethacin inhibited the both of sodium arachidonate or ADP induced platelet aggregation, imidazole only inhibited sodium arachidonate induced aggregation.

In the mean time, around 10 kinds of phenolic acids are reported to be contained in Ginseng, among them, maltol and salicylic acid which have antioxidant effect, and trans-p-coumarid acid wich is not an antioxidant, were subjected to in this study.

Table 4. Effects of some phenolic acids on the biosynthesis of PGs in HPH

Compound	Levels of PGs (%, M±S.D.)					AA (%)
	Total	PGE_2	$PGF_{2\alpha}$	TxB_2	6-keto-$PGF_{1\alpha}$	
Control	23.2±2.5	5.1±0.8	3.1±0.5	9.7±3.8	6.3±0.8	36.0±4.9 (17)
Maltol 1 mM	20.4±4.0	4.7±0.7	2.2±0.4*	8.9±1.2	4.7±0.7*	80.4±10.2 (5)
p-Coumaric acid 1 mM	11.9±2.3*	3.5±0.7	1.0±0.2*	3.7±0.5*	3.7±0.6*	42.8±6.3 (5)
Salicylic aicd 1 mM	22.4±3.1	5.4±0.8	1.7±0.3*	9.3±1.0	6.0±0.9	34.9±5.8 (5)
Imidazole 5 mM	30.2±5.1	11.4±2.0*	5.4±0.7*	5.4±0.7*	8.0±1.0*	38.2±5.0 (10)

( ) represents number of experiments.
*; $P<0.05$

Total prostaglandin formation by various enzyme source such as RKM, BAM, HPH were not affected by maltol and salicylic acid but significantly inhibited by p-coumaric acid.

p-coumaria acid also inhibit the formation of $PGF_{2\alpha}$, TxB_2, and 6-Keto $PGF_{1\alpha}$ in HPH reaction system.

Platelet aggregation induced by U46619 was significantly inhibited by p-coumaric acid but the effects of maltol and salicylic acid on platelet aggregation were not different from that of control.

In conclusion, these findings suggest that both of Ginseng saponins and phenolic acids seem to play a role in the regulation of the arachidonic acid metabolism and phenolic acids may act on cycloxygenase directly while Ginseng saponins probably affect the divergent synthetic pathway of prostaglandins from endoperoxide.

References

1. Altura, B.M. and Altura, B.T.: Vascular smooth muscle and prostaglandins, Fed. Proc., **35**(12), 2360.
2. Brune, K., Glatt, M. and Kalin, H.: Pharmacological control of prostaglandin and thromboxane release from macrophages, *Nature*, **274**, 261 (1978).
3. Hamberg, M., *et al.*: Prostaglandin endoperoxides, Novel transformation of arachidonic acid in human platelets, *Proc. Natl. Acad. Sci. USA.*, **71**(9), 3400 (1974).
4. Han, B.H., *et al.*: Studies on the antioxidant components of Korean Ginseng-(III) Identification of phenolic acids, *Arch. Pharm. Res.*, **4**(1), 53 (1981).
5. Suchen Hong, L., *et al.*: Tranylcypromine and 15-hydroperoxy arachidonic acid release in addition to inhibition of prostacyclin synthesis in calf aortic endothelial cells, *J. Biol. Chem.*, **255**(20), 9538 (1980).
6. Nicolaou, K.C., *et al.*: Synthesis and biological properties of pinanethromboxane A_2, a selective inhibitor of coronary artery constriction, platelet aggregation, and thromboxane formation, *Proc. Natl. Acad. Sci. USA.*, **76**(6), 2566 (1979).
7. Svensson, J., *et al.*: Prostaglandin endoperoxides. IX. Characterization of rabbit aorta contracting substance from guinea pig lung and human platelets, *Acta. Physiol. Scand.*, **94**, 222 (1975).