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# The Effect of Ginseng Saponins on the Biosynthesis of Prostaglandins

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## Abstract

The effects of ginseng saponins and some phenolic acids on the *in vitro* biosynthesis of prostaglandins was examined in order to identify the role of some ginseng components on the regulaion of arachidonic acid metabolism. The productions of prostaglandin $E_2$($PGE_2$), prostaglandin $F_2\alpha$($PGF_2\alpha$), thromboxane $B_2$($TxB_2$) and 6-keto-prostaglandin $F_1\alpha$(6-keto-$PGF_1\alpha$) from [$^3$H]-arachidonic acid were evaluated with rabbit kidney microsome, human platelet homogenate and bovine aortic microsome. The amounts of the total cyclooxygenase products from arachidonic acid did't show significant changes in the presence of ginseng saponins. Panaxadiol, panaxatriol and all of the ginsenosides used in these experiments reduced the formation of $TxB_2$, while increased the 6-keto-$PGF_1\alpha$ production dose dependently. Ginseng saponins did't inhibit the ADP(10μM) induced platelet aggregation, but sodium arachidonate (0.5 mM) induced platelet aggregation, but sodium arachidonate (0.5 mM) induced platelet aggregation was significantly inhibited. These findings suggest that ginseng saponins seem to play a role in the regulation of the arachidonate metabolism, probably by affecting the divergent biosynthetic pathway of prostaglandins from endoperoxide.

## Introduction

Modern pharmacological studies on the effects of ginseng could be summerized as (Hong et al. 1979). The multifarious pharmacological action of ginseng, such as effect on central nervous system, cardiovascular system, metabolic activity of body, hematopoietic system, gastrointestinal tract and even on stress or cancer, 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.

## Meterial and Methods

The products of arachidonic acid metabolism using various enzyme sources, rabbit kidney microsome (Morrison et al., 1978), human platelet homogenate (Haurand et al., 1985) and bovine aortic microsome (Moncada et al. 1976) were evaluated with $PGE_2$, $PGE_2\alpha$, $TxB_2$ and 6keto-$PGE_1\alpha$ production from $^3$H-arachidonic acid determined by thin layer chromatography (Fig. 1).

## Results

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

| Addition Source | Cyclooxgenase Products Converted (%) | | |
|---|---|---|---|
| | RKM | BAM | HPH |
| Control | 18.65± 2.09 | 16.68± 1.75 | 23.17± 2.53 |
| Panaxadiol 500 ug/ml | 15.69± 4.21 | 20.21± 2.35 | 22.43± 2.68 |
| Panaxatriol 500 ug/ml | 15.55± 4.03 | 17.82± 2.19 | 22.61± 2.98 |
| G-$Rb_2$ 500 ug/ml | 16.94± 1.98 | 17.43± 2.02 | 19.35± 2.12 |
| G-Rc 500 ug/ml | 19.09± 1.65 | 20.38± 2.59 | 17.06± 2.54 |
| G-Re 500 ug/ml | 20.67± 2.11 | 18.84± 1.58 | 21.60± 2.18 |

The amounts of total cyclooxygenase products produced by various enzyme sources did not show any significant changes in the presence of ginseng saponins (Table 1).

But each divergent prostaglandin productions are influenced by Ginseng saponins. Both panaxadiol or panaxatriol increased the 6keto-$PGF_1\alpha$ production and suppressed the $PGF_2\alpha$ and $TxB_2$ production but $PGE_2$ production was not influenced significantly (Fig. 2).

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 signifi-

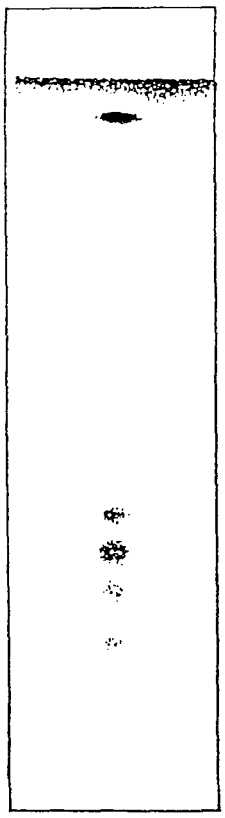


Fig. 1. TCL pattern of authentic PG standards.
Solvent : ethylacetate : acetic acid : trimethylpentane : D.W. =11 : 2 : 5 : 10

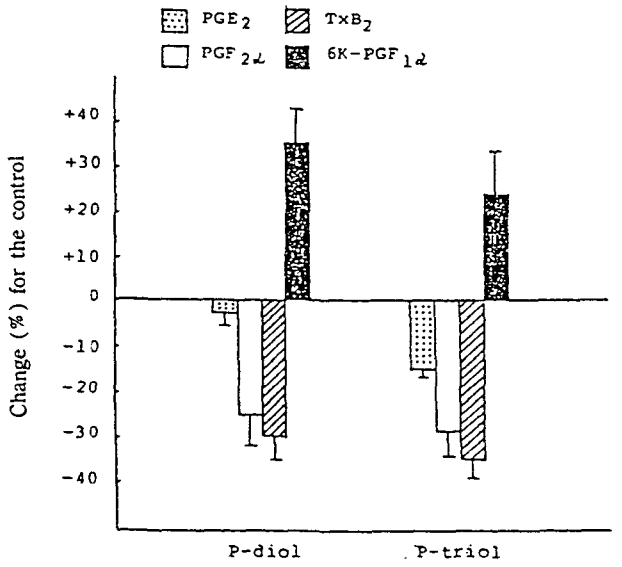


Fig. 2. Effects of panaxadiol and panaxatriol ($5\times10^{-4}$ g/ml) on arachidonate metabolite formation.

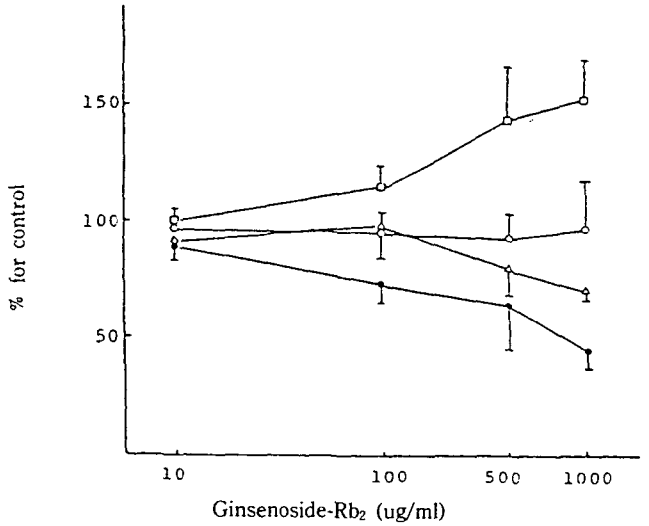


Fig. 3. Effect of G-$Rb_2$ on arachidonate metabolite formation. Each point represents as the percentage for the control. Each points were mean of 5 experiments.

(○) $PGE_2$; (△) $PGF_2\alpha$; (●) $TxB_2$; (⊏) 6-keto-$PGF_1\alpha$.

cantly influenced by ginsenoside $Rb_2$ in concentration of 10 to 1000 ug/ml (Fig. 3).

In the presence of ginsenoside Rc, the production of 6keto-$PGF_1\alpha$ was increased but that of $PGF_2$, $PGF_2\alpha$ and $TxB_2$ were decreased dose-dependently (Fig. 4).

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 $PGF_2$ and $PGF_2\alpha$ were not affected (Fig. 5).

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 equivalent with that of imidazole in a concentrations of 2 mM (Fig. 6).

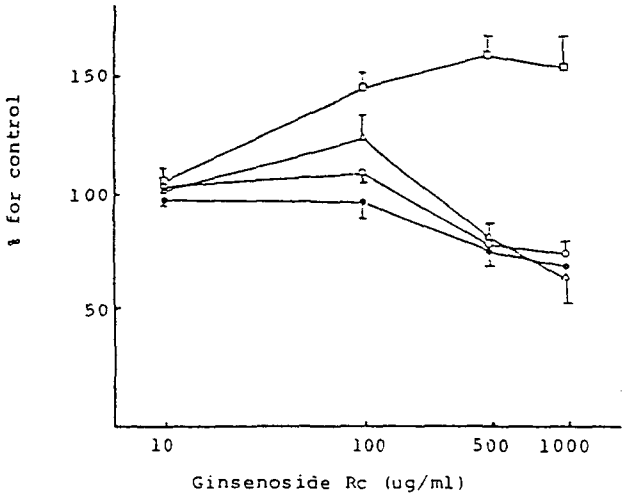


Fig. 4. Effect of G-Rc on arachidonate metabolite formation. Each point represents as the percentage for the control. Each points were mean of 5 experiments.

(○) $PGE_2$; (△) $PGF_2\alpha$; (●) $TxB_2$; (⊏) 6-keto- $PGF_1\alpha$.

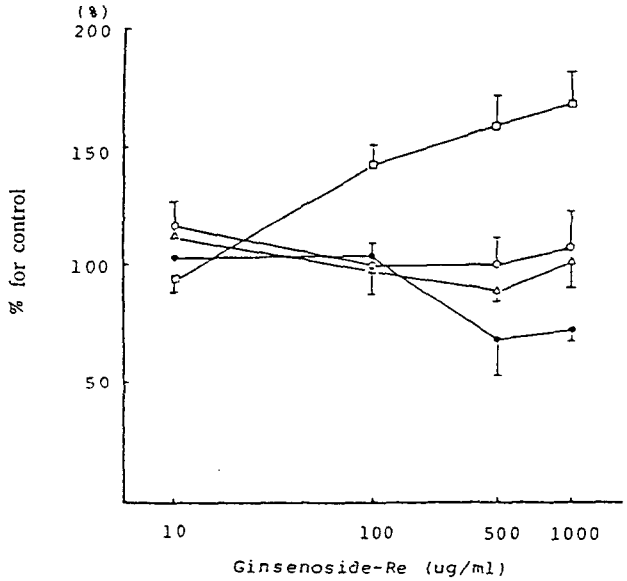


Fig. 5. Effect of G-Re on arachidonate metabolite formation. (○) $PGE_2$; (△) $PGF_2\alpha$; (●) $TxB_2$; (⊏) 6-keto-$PGF_1\alpha$.

And ginseng saponins seems to potentiate the effect of imidazole additively (Fig. 7).

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-$PGE_1\alpha$ was nearly compeletely reversed by ginsenosides (Table 2.)

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 aggregation was significantly inhibited by all the ginseng saponins tested except ginsenoside $Rb_1$ 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 (Table 3).

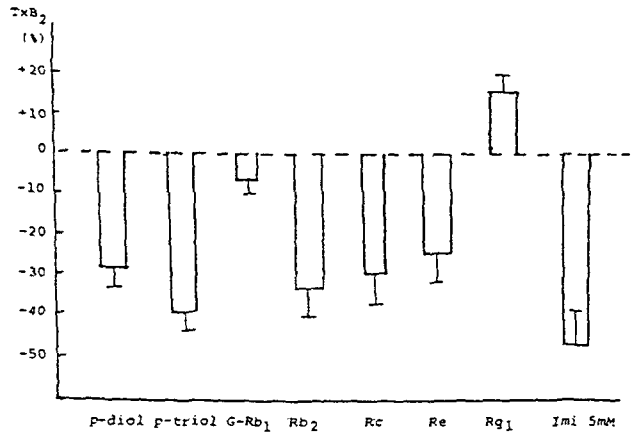


Fig. 6. Effects of ginseng saponins (500ug/ml) on $TxB_2$ formation in HPH compared with imidazole (5mM).

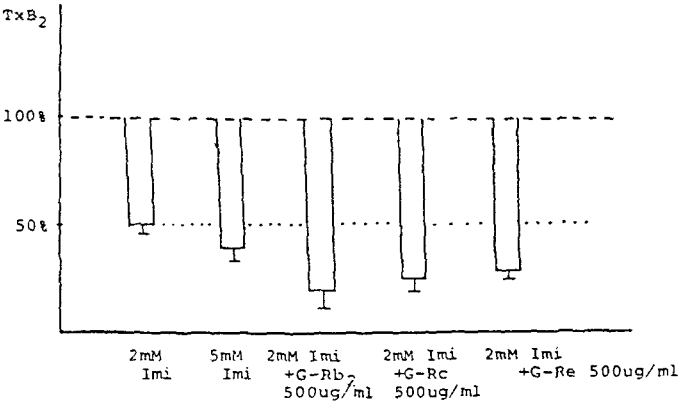


Fig. 7. Combination effect of ginsenosides (each conc., 500ug/ml) and imidazole in HPH.
HPH (1mg protein in 1.0 ml Tris-HCl buffer, ph 7.4) were incubated with arachidonic acid ([$^3$H]-AA, 0.5 uCi, 0.5 mM) in the presence of imidazole only or imidazole + ginsenoside. Data shown are the change for the control.

## References


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**H. Saito:** As you know there are three different types of saponins, panaxadiol, panaxatriol, and oleanolic acid glycosides. Ginsenoside Ro, oleanolic acid glycoside contained in ginseng, was effective in my antiinflammatory experiments. I hope you use GRo in your series of experiment.

**C.W. Park:** Thank you very much for your suggestions. I will try it in the nearest future.

**F. Sandberg:** Can you draw any conclusion from your experiments as regard to clinical effect in the inflammation?

**Table 2.** Effects of ginsenoside on the biosynthesis of prostacyclin in the presence of tranylcypromine in BAM

| Pretreatment | | 6K-PGF$_{1\alpha}$ % conversion from [$^3$H]-AA |
|---|---|---|
| Tranylcypromine | 0 | 8.73 (100%) |
| | 0.1 mM | 8.48 (97.1%) |
| | 1 mM | 7.20 (82.5%) |
| | 5 mM | 3.95 (45.3%) |
| | 10 mM | 2.65 (30.4%) |
| -Tranylcypromine 5 mM | + G-Rb$_2$ $5\times10^{-4}$ g/ml | 6.83 (78.2%) |
| | + G-Rc $5\times10^{-4}$ g/ml | 8.58 (98.3%) |
| | + G-Re $5\times10^{-4}$ g/ml | 8.84 (101.3%) |

Table 3. Effects of some ginsenosides on human platelet aggregation induced by ADP and arachidonate

| Addition Stimulant | % light transmission | |
|---|---|---|
| | ADP (10 uM) | AA-Na (1mM) |
| Control | 77.5± 2.9 | 74.00± 5.0 |
| Pretreatment | | |
| imidazole 5mM | 64.59± 4.8 | 15.63± 3.1* |
| Indomethacin 40 uM | 51.25± 4.1* | 26.25± 5.2* |
| P-diol 0.5 mg/ml | 74.38± 3.5 | 17.5± 3.3* |
| P-Triol 0.5 mg/ml | 78.75± 5.9 | 21.25± 6.8* |
| G-Rb$_1$ 0.5 mg/ml | 71.25± 4.7 | 71.88± 5.9 |
| G-Rb$_2$ 0.5 mg/ml | 74.38± 5.8 | 18.13± 5.1* |
| G-Rc 0.5 mg/ml | 78.13± 4.5 | 16.25± 4.8* |
| G-Re 0.5 mg/ml | 74.25± 3.6 | 36.25± 9.7* |
| G-Rg$_1$ 0.5 mg/ml | 70.00± 5.7 | 14.38± 4.5* |

Aggregation was measured as percent light transmission. Values are Mean± S.D. of 3 experiments performed in PRP (Platelet Conc; 3-3.5$\times10^5$/ul.) preincubated with drugs for 15 min at 37°C.
*; $p<0.005$, as compared to control.

In conclusion ginseng saponin seems to play a role in the regulation of arachidonic acid metabolism, in which ginseng saponin increase the prostacyclin and decrease the thromboxane production probably by affecting the divergent metabolic pathway of prostaglandins from endoperoxide but not by affecting arachidonic acid metabolism through cyclooxygenase

**C. W. Park:** I am not sure but clinical effect of ginseng in the inflammation may be related to this results.

**R. R. Bridges:** The concentration of ginsenosides utilized to inhibit the production of prostaglandins and thromboxans appeared to be quite high. Are these concentrations too high to represent physiologic concentrations in individuals taking ginseng?

**C. W. Park:** Yes, I agree with you. The concentrations of ginsenosides used in this experiment was quite higher than physiological concentration.

**H. Oura:** Did you investigate the effect of $Rg_1$ on platelet aggregation?

**C. W. Park :** Unfortunately, I did not.

## 인삼 Saponin이 Prostaglandin 대사에 미치는 영향

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인삼의 효과는 인삼칠효설로 요약되듯이 각종 장기에 대하여 다양한 약리작용을 나타낸다. 이는 인삼의 약리작용을 중개하는 생체내 생리활성물질의 존재를 생각하게 되며 이같이 생리활성물질의 하나로 prostaglandin 을 들 수 있다.

본 연구에서는 인삼성분이 prostaglandin 등 arachidonic acid 대사산물 생성에 미치는 영향을 실험함으로써 인삼의 약리학적 작용과 그 기전을 간접적으로 구명하고자 하였다. 즉 [$^3$H]-arachidonic acid를 기질로 넣어주고 토끼 신장 microsome, 소 대동맥 microsome , 사람 혈소판 homogenate 등을 효소원으로 한 in vitro 생합성과정에 변화를 주는 수종 인삼 saponin 및 phenolic acid 성분의 효과를 검정하였다. 실험에 사용한 인삼 saponin 성분은 panaxadiol, panaxatriol 및 protopanaxadiol 계 saponin 류인 ginsenoside $Rb_2$(G-$Rb_2$), ginsenoside Rc(G-Rc) 및 protopanaxatriol 계 saponin 류인 ginsenoside Re(G-Re) 이었고 이들 성분이 arachidonic acid 로부터 cyclooxygenase를 통해 최종 대사산물인 prostaglandin 류를 생성하는 과정에 미치는 영향을 관찰하여 다음과 같은 결과를 얻었다.

1. Arachidonic acid 로부터 생성된 총 cyclooxygenase 반응생성물 및 malondialdehyde의 양은 실험에 사용한 인삼 saponin 성분의 전 농도 범위에서 유의적인 변화를 보이지 않았는데 이는 인삼 saponin 성분들은 cyclooxygenase에 직접 작용하지 않는다는 것을 설명해 준다.

2. Panaxadiol (500 μg/ml)은 $PGE_2$ 생성에는 영향이 없으나 $PGF_{2\alpha}$ 및 $TxB_2$의 생성을 감소시켰으며 동시에 6-keto-$PGF_{1\alpha}$의 생성은 증가시켰다. Panaxatriol 도 유사한 양상을 보였다.

3. G-$Rb_2$및 G-Rc는 $PGE_2$ 및 $PGF_{2\alpha}$생성에 유의적인 차이를 보이지 않으나 농도의존적으로 $TxB_2$의 생성을 감소시켰고 6-keto-$PGF_{1\alpha}$ 의 생성을 증가시켰는데 이는 $TxA_2$ synthetase 억제제인 imidazole 의 효과와 유사하였다.

4. G-Re는 $1\times10^{-5}$g/ml 이하의 농도에서는 효과가 없으나 $1\times10^{-4}$ g/ml 이상의 농도에서 농도의존적으로 유의성 있는 $PGE_2$, $PGF_{2\alpha}$, $TxB_2$의 생성억제와 함께 6-keto-$PGF_{1\alpha}$ 증가를 보였다. 이는 prostacyclin synthetase를 자극하는 serotonin의 효과와 같은 작용으로서 prostacyclin synthetase 억제제인 tranylcypromine에 대하여 길항효과를 보였다.

5. $TxB_2$생성억제 작용을 나타내는 ginsenoside들의 효과를 뒷받침하기 위하여 인삼 saponin 성분을 전처치한 platelet rich plasma에서 혈소판 응집시험 결과, ADP로 유도된 혈소판 응집반응에는 모든 인삼 saponin 성분들이 효과가 없었으나 arachidonic acid로 유도된 혈소판 응집반응에는 G-$Rb_2$, G-Rc, G-Re의 순으로 농도의존적인 억제현상을 보였다.

이상의 결과와 같이 인삼 saponin 성분들은 arachidonic acid로부터 cyclooxygenase를 통해 일단 생성된 endoperoxide에서 각각의 prostaglandin을 생성하는 효소, 특히 G-$Rb_2$는 $TxA_2$ sysnthetase에 강력한 억제제로, G-Re는 prostacyclin 생합성의 촉진제로 심혈관계 균형에 기여하리라 생각된다.