# Cancer Chemopreventive Effects of Ginsenoside $Rg_3$, $Rg_5$, $Rh_2$ and BST from Enzymatically Fermented Korean Ginseng Extract

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**Abstract**

*Panax ginseng* C. A. Meyer has been one of the most highly recognized medicinal herbs in the Orient. Previous experiments have demonstrated that $Rg_3$ and $Rg_5$ statistically significantly decreased the incidence of benzo(a)pyrene-induced mouse lung tumor, $Rh_2$ showed tendency of decrease and $Rh_1$ showed no effect. It was, therefore, concluded that $Rg_3$, $Rg_5$ and $Rh_2$ are active cancer chemopreventive components in red ginseng and they either singularly or synergistically act in the prevention of cancer.

This study was undertaken to compare the cancer chemopreventive effects of $Rg_3$, $Rg_5$ and $Rh_2$ (purity: more than 60%) isolated from fermented ginseng extract and BST fermented ginseng with fortified ginsenoside $Rg_3$ and $Rh_2$. The cancer chemopreventive effects were investigated in experimental groups treated with benzo(a)pyrene(BP) with ginsenoside $Rg_3$, $Rg_5$, $Rh_2$ or BST at three doses of 50°C/ml, 100°C/ml and 200°C/ml When mice given with 50°C/ml concentration of ginsenoside $Rg_3$ combined with BP for 6 weeks after BP administration, $Rg_3$ showed 60% of lung tumor incidence, where as 100°C/ml and 200°C/ml of $Rg_3$ combined with BP groups had significant decrease of incidence (40.0%) respectively, with the inhibition rate being 35.5%.

While the tumor incidence was not decreased in the group treated with BP and 50 of $Rg_5$, the incidence was 34.0% and 32.0% in the group treated with BP and 100 and 200 of $Rg_5$, respectively. These incidences were significantly less than the group treated with BP alone, with the inhibition rate being 45.2% and 48.4%, respectively. On the other hand, in the group treated with BP and 50 of ginsenoside $Rh_2$, the tumor incidence was not decreased. However, the incidence was 40.0% and 38.8% in the experimental treated with BP and 100 and 200 of $Rh_2$, respectively, with the inhibition rate being 45.2% and 48.4%, respectively. In addition, the incidence showed the tendency to decrease in the experimental group treated with BP and 50 of BST which contained 16.2% of $Rh_2$, 15.4% of $Rg_3$ and 2.5% of $Rg_5$. The tumor incidence was 54.0% in this

group. In the group treated with 100 and 200 of BST, the incidence was 34.0% and 30.0%, respectively, the incidences significantly being lower than the group treated with BP alone, with the inhibiting rate being 45.2% and 51.6%, respectively.

The results of this study strongly suggested that ginsenoside $Rg_3$, $Rg_5$ and $Rh_2$ are the active components of red ginseng having a cancer chemopreventive activity and $Rg_5$ is the strongest cancer chempopreventive among them. On the other hand, the results demonstrating that the incidence of lung tumor was more markedly reduced by BST fermented ginseng with fortified ginsenoside $Rh_2$ or $Rg_3$ compared to the single component alone, suggest that the combination of these components may remarkablely improve the cancer preventive effect.

**Key words:** Cancer chemoprevention, benzo(a)pyrene, lung tumor, fermented ginseng extract, gisenoside $Rg_3$, ginsenoside $Rh_2$ or ginsenoside $Rg_3$, fortified ginsenoside BST.

## Introduction

Despite comprehensive advances in early diagnosis of cancer and chemotherapy for cancer, many cancers still remain difficult to cure(1,2). Primary cancer prevention, particularly chemoprevention, becomes an increasingly useful strategy for the fight against cancer(3). The ginseng root has been used empirically for thousands of years in many Asian countries(4). We have proposed that the life-prolonging effect of ginseng described by Shennong(5) during the Liang Dynasty in China may be due to the preventive activity of ginseng against the development of cancers.

### *Long-term anticarcinogenicity experiments of red ginseng*

Employing a long term carcinogenesis model using newborn mice(6,7), we carried out extensive experiments in 1978 to investigate whether ginseng inhibited carcinogenesis, and demonstrated that the red ginseng extracts of Panax ginseng C.A. Meyer cultivated in Korea had anticarcinogenic activity against lung tumor and liver cancer induced by urethane or aflatoxin $B_1$. The extract was found to be partly involved in the elevation of natural killer cell activity(8), the results providing the hope for natural products preventing human cancers.

### *Nine-week Medium-term anticarcinogenicity experiments*

The medium-term (9 weeks) model system also revealed anticarcinogenicity of ginseng for

pulmonary adenoma induced by benzo(a)pyrene (BP) in newborn mice(9-12). Employing BP as carcinogen, we further investigated whether fresh ginseng or white ginseng had the similar anti-carcinogenic effects, and whether the anticarcinogenic effects depended on the types and ages of ginseng. We found a significant anticarcinogenic effect of 6-year old dried powder or fresh ginseng extract, 5- and 6-year old white ginseng powder or extract, and 4-, 5- and 6-year old red ginseng powder or extract(13-15). The results demonstrated that the anticarcinogenicity was more prominent in aged or heat treated extract of fresh ginseng and red ginseng prepared by steaming.

***Epidemiological study in ginseng intakers***

In light of the above described evidences, in 1987 we began a case-control study with 905 pairs to confirm whether red ginseng extracts had as much anticarcinogenic effect on human cancers as on mice. We later extended the number of subjects from 905 pairs to 1,987 pairs. A prospective study was started 6 months after the first case-control study among the population residing in ginseng cultivation area to find out whether ginseng intake prevents the cancers and what types of cancer can be prevented.

***Case-control study of 905 pairs in cancer hospital***

The effect of ginseng consumption on the risk for cancer was investigated by interviewing 905 pairs of cases and controls matched by age, sex and date of admission to the Korea Cancer Center Hospital, Seoul, Korea(16). Of the 905 cases, 562 (62%) had a history of ginseng intake compared to 674 (75%) of the controls, which was statistically significant difference ($p<0.01$). The odds ratio (OR) of cancer in relation to ginseng intake was 0.56 [95% confidence interval (CI), 0.45-0.69]. Ginseng extract and powder were shown to be more effective than fresh sliced ginseng, juice or tea in reducing the ORs. These results strongly support the hypothesis that ginseng has cancer preventive effects as suggested by the previous animal experiments. The Lancet stated in an editorial that ginseng consumption reduces the risks for all cancer types. The article included an example of the "non-organ specific approach" to cancer chemoprevention(17).

***Case-control study of 1,987 pairs in cancer hospital***

In extended case-control study with 1,987 pairs(18), the ORs for cancer were 0.37 in fresh ginseng extract users, 0.57 in white ginseng extract users, 0.30 in white ginseng extract users, 0.30 in white ginseng powder users and 0.20 in red ginseng users. Those who took fresh ginseng

slices, fresh ginseng juice and white ginseng tea, however, did not show decrease in the risk. Overall, the risk decreased as the frequency and duration of ginseng intake increased. With respect to the site of cancer, the ORs for cancers of lip, oral cavity, pharynx, esophagus, stomach, colorectum, liver, pancreas, larynx, lung and ovary were significantly reduced by ginseng intake. Smokers with ginseng intake showed lower ORs for cancers of lung, lip, oral cavity and pharynx and liver than those without ginseng intake.

***Cohort study in Kangwha-eup population***

In 5 year follow-up cohort study conducted in the ginseng cultivation area, Kangwha-eup(19), ginseng intakers had significantly lower risk than non-intakers. As for the type of ginseng, cancer risk significantly decreased among intakers of fresh ginseng extract, alone or together with other ginseng preparations. Among 24 red ginseng intakers, no cancer death occurred during the follow-up period. The risk for stomach and lung cancers was significantly reduced by ginseng intake, showing a statistically significant dose-response relationship in each follow-up year. In conclusion, Panax ginseng C.A. Meyer has been established as non-organ specific cancer preventive, having dose response relationship(20,21).

***Active chemoprevention compounds in red gunseng***

These results warrant that ginseng extracts and its synthetic derivatives should be examined for their anticarcinogenic effect on carcinogen-induced mice lung tumors. To investigate the active components for cancer prevention, several fractions of 6-year old fresh ginseng and red ginseng(22), four semi-synthetic ginsenoside $Rh_1$, $Rh_2$, $Rg_3$ and $Rg_5$, and major saponin components in red ginseng were examined. Among the ginsenosides, $Rg_3$ and $Rg_5$ showed significant reduction of lung tumor incidence and $Rh_2$ had a tendency of decreasing in the incidence. Ginsenoside $Rg_3$, $Rg_5$ and $Rh_2$ were found to be active anticarcinogenic compounds(23,24).

***Purpose of present study***

Ginsenoside $Rg_3$, $Rg_5$ and $Rh_2$ were reported to be some of the active components having anticarcinogenic activity. This study was undertaken to compare the anticarcinogenic effects of $Rg_3$, $Rg_5$ and $Rh_2$ isolated from fermented ginseng extract and fermented ginseng with fortified ginsenoside $Rg_3$, $Rh_2$(BST).

## Materials and Methods

### *Experimental animals*

ICR mice were obtained from Korea Institute of Experimental Animals, Eumsung, Korea and bred at random inter se. All mice were housed in a controlled room, fed solid pellets and given water ad libitum.. Newborn mice within 24 hours after birth were used. Each group comprised 25 male and 25 female weaned mice respectively.

### *Red ginseng*

Red ginseng of Panax ginseng C. A. Meyer cultivated in Korea was obtained from Korea Ginseng Corporation, Daejon, Korea.

### *Carcinogen*

Chemical carcinogen used in the experiment was benzo(a)pyrene (BP) purchased from Sigma Chemical Co., USA.

### *Ginsenosides*

Ginsenosides $Rh_2$, $Rg_3$, $Rg_5$ and BST were kindly supplied by the Biosapogen Technology Co., Ltd. Seoul, Korea. Ginsenoside $Rh_2$, $Rg_3$ and $Rg_5$ isolated from fermented ginseng extract, under acidic hydrolysis from protopanaxadiol-type ginsenoside using β-glucosidase, a saponin hydrolytic enzyme, obtained from *Aspergillus sp.*

The putity of the $Rh_2$, $Rg_3$ and $Rg_5$ was more than 60%. BST was fermented ginseng with fortified ginsenoside $Rh_2$ and $Rg_3$ which was composed of 16% ginsenoside $Rh_2$, 15% ginsenoside

Material specification

| Ginsenoside | Component (%) | | |
|---|---|---|---|
| | $Rh_2$ | $Rg_3$ | $Rg_5$ |
| Ginsenoside $Rh_2$ | 61.4 | 1.8 | 1.2 |
| Ginsenoside $Rg_3$ | 0.8 | 62.5 | 1.4 |
| Ginsenoside $Rg_5$ | 0.9 | 2.3 | 60.3 |
| BST(fortified $Rh_2$, $Rg_3$) | 16.2 | 15.4 | 2.5 |

All materials were included aglycon, sugar and other ginsenosides.

$Rg_3$ and 2.5% ginsenoside $Rg_5$.

**Anticarcinogenicity assay by Yun's 9-week medium-term anticarcinogenicity test model.** The present experiment adopted the 9-week medium-term bioassay model established in the laboratory and called Yun,s anticarcinogenicity test to distinguish this test from other medium-term bioassay models. ICR newborn mice less than 24 hours old were injected at a dose of 0.02 ml of benzo(a)pyrene (0.5 mg suspension of BP in olive oil) once subcutaneously in the scapular region. After weaning, test materials were administered for 6 weeks through drinking water(9-12).

***Control groups***

There were five control groups including normal, ginsenosside $Rg_3$, $Rg_5$, $Rh_2$, BST alone without carcinogen and benzo(a)pyren(BP) alone and BP combined with red ginseng extract with carcinogen.

***Experimental groups***

The anticarcinogenic effects were investigated in experimental group treated with BP with ginsenoside $Rg_3$, $Rg_5$, $Rh_2$ or BST at three doses of 50°C/ml, 100°C/ml and 200°C/ml. Experimental groups consist of four main groups ($Rg_3$, $Rg_5$, $Rh_2$ and BST) including 3 doses groups, resulting in 12 total experimental groups. Immediately after weaning, ginsenosides were given in drinking water for 6 weeks.

***Sacrificing animals***

All mice were sacrificed at the ninth week after birth. Lungs were excised and fixed in Tellyesniczky solution (100 ml of 70% ethanol, 3 ml of formalin, 5 ml of glacial acetic acid). Then the adenomas were counted by the naked eye. After counting, the lungs were embedded in paraffin, cut and then stained with hematoxylin-eosin.

***Scoring of lung tumors***

To obtain an index of tumor incidence, the percentage of tumor bearing mice per total number of mice in each group was calculated. Tumor multiplicity was defined as the average number of tumors per mouse obtained by dividing the total number of tumors by the total number of mice per group including non-tumor bearing animals. Statistical comparisons were made using the Chi-square test for tumor incidence and Students test for multiplicity. A null hypothesis was

rejected whenever a P value of 0.05 or less was found.

## Results

***Findings of mortality, body weight and lung tumor incidence between groups***

There was no mortality attributable to the treatment and overall weight gain over the 9 week period was almost the same between control and treated mice. Mean relative lung weight of each group did not show any differences among groups. In normal control group, the incidence of lung adenoma was 2.0%(1/50). Among groups given singularly with ginsenoside, $Rg_3$, $Rg_5$, $Rh_2$ and BST, $Rg_3$ group showed 2.0% of lung tumor incidence.

***Tumor incidence of benzo(a)pyrene treated group and red ginseng extract combined group***

The incidence of lung tumor was 62% in control group who was administered with BP alone. In the experimental group treated with BP and red ginseng, the incidence of lung tumor was 44%, which was significantly lower than that of control group, with the inhibition rate being 29%.

***Tumor incidence of ginsenoside $Rg_3$ combined group***

Tumor incidence was not reduced in the group treated with 50 of $Rg_3$. In the group treated with 100 and 200 of Rg3, however, the incidence 40% respectively, which was significantly lower than the group treated with BP alone, with the inhibition rate being 35.5%.

***Tumor incidence of ginsenoside $Rg_5$ combined group***

While the tumor incidence was not decreased in the experimental group treated with 50 of $Rg_5$, the incidence was 34.0% and 32.0% in the experimental group treated with 100 and 200 of $Rg_5$, respectively. These incidences were significantly less than the group treated with BP alone, with the inhibition rate being 45.2% and 48.4%, respectively.

***Tumor incidence of ginsenoside $Rh_2$ combined group***

In the group treated with BP and 50 of ginsenoside $Rh_2$, the tumor incidence was not decreased. However, the incidence was also significantly decreased to 40.0% and 38.8% in the experimental group treated with 100 and 200 of $Rh_2$, respectively, with the inhibition rate being 45.2% and 48.4%, respectively.

***Tumor incidence of BST combined group***

On the other hand , the incidence showed the tendency to decrease in the group treated with 50 of BST which contained 16.2% of $Rh_2$, 15.4% of $Rg_3$ and 2.5% of $Rg_5$. The tumor incidence was 54.0% in this group. In the group treated with 100 and 200 of BST, the incidence was 34.0% and 30.0%, respectively, the incidences significantly being lower than the group treated with BP alone, with the inhibiting rate being 45.2% and 51.6%, respectively.

## Discussion

Our strategy at this moment is to switch from therapeutic approaches to chemoprevention of cancer by identifying effective natural products. Anticarcinogenic effects of Korean red ginseng was earlier observed in 1980 by long-term (6, 7) or medium-term model (Yun's model) (9-12) with mouse lung tumor. We observed that anticarcinogenicity of ginseng was dependent on the type and age of ginseng (13,14). In two attempts of human case-control studies (16,18) and a cohort study (19) to evaluate the cancer preventive effect, however, fresh ginseng was found to be ineffective to decrease in the relative risk (RR). On the other hand, when treated with heat, fresh ginseng, white ginseng and red ginseng were significantly effective in reducing the RRs, which was similar to the results obtained from animal experiments. This result suggested the active cancer chemopreventive compounds can be generated from Korean ginseng by heat-treatment.

At present, 35 ginsenosides have been identified in ginseng and 12 ginsenosides were found in red ginseng (20). We prepared four ginsenosides from Korean red ginseng and tested their chemopreventive effect in Yuns model. This model has been successfully employed to confirm anticarcinogenicity effect of ginseng on lung tumor incidence induced by benzo(a)pyrene in mice. Mouse lung tumor model has been highly recommended for preclinical as well as clinical test models (25, 26), because this model showed no anticarcinogenicity with not only -carotene and 13-cis retinoic acid (10-12, 27), but also genetic alteration in mouse lung tumor which was similarly to that of human lung cancer cancer cells.

This fact led to search biologically active components in ginseng, and they so far identified 35 ginsenosides in general and 12 in red ginseng (20).

Some of the ginsenosides are present in red ginseng in such a minute quantity, so that it is extremely difficult to obtain the amount enough for in vivo assay. Nevertheless, we succeeded to purify and identify four ginsenosides, including ginsenoside $Rh_1$, $Rh_2$, $Rg_3$ and $Rg_5$. Among the

four ginsenosides, $Rg_3$ and $Rg_5$ showed significant reduction of lung tumor incidence and $Rh_2$ had a tendency of decreasing in the incidence. These results strongly indicated that the anticarcinogenicity or human cancer preventive effect of ginseng is due to ginsenoside $Rg_3$, $Rg_5$ and $Rh_2$.

As $Rg_3$, $Rg_5$ and $Rh_2$ were reported to be the active components for anticarcinogenic activity, we have conducted this study to compare the anticarcinogenic effects of $Rg_3$, $Rg_5$ and $Rh_2$ isolated from fermented ginseng extract and fermented ginseng with fortified ginsenoside $Rg_3$ and $Rh_2$ (BST). The results of this study strongly suggested that ginsenoside $Rg_3$, $Rg_5$ and $Rh_2$ are the active components of red ginseng having anticarcionogenic activity and $Rg_5$ is the strongest anticarcinogenicity among them. On the other hand, the results demonstrating that the incidence of lung tumor was more markedly reduced by combined use of BST with $Rh_2$ or $Rg_3$ compared to the single component alone, suggest that the combination of these components may remarkablely improve the cancer preventive effect.

Although the mechanism of how these three minor ginsenosides exhibit the anticarcinogenic effect is not clear, it is highly likely that three ginsenosides are involved in the effect. It is quite templing to suggest that the ginsenosides may target one of the five steps of either Vogelstein's multi-stage carcinogenesis or inactivation of suppressor genes (28).

In conclusion, epidemiological studies including case-control studies (16,18) and population based cohort study (20) clearly demonstrated that the heat-treated red ginseng is very effective in preventing cancer in a non-organ specific manner (18-20,29). In order to further confirm these ginsenosides as non-organ specific cancer preventives, it is needed to obtain these compounds as a commercial scale for the clinical trial as well as further experimental studies.

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