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Inhibitory Effects of *Kochujang* Extracts on the Tumor Formation and Lung Metastasis in Mice

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Abstract

Effects of *kochujang* (Korean red pepper soybean paste) extracts on tumor formation, natural killer (NK) cell activity in spleen and glutathione *S*-transferase (GST) activity in liver were investigated in the sarcoma-180 cell transplanted mice. Inhibitory effects of these samples on lung metastasis of colon 26-M3.1 cells were also evaluated in the Balb/c mice. The injection of methanol extracts from traditional *kochujang* I (TK I , 0-day fermented), II (TKII, 6-month fermented), commercial *kochujang* (CK, 1-month fermented) and red pepper powder (RPP) significantly reduced tumor formation in Balb/c mice ($p<0.05$). TKII decreased tumor growth by 46% compared with control, resulting in the smallest tumor weight. The transplantation of sarcoma-180 cells increased the spleen/body weight ratio of Balb/c mice, while TKI and TKII significantly decreased this index ($p<0.05$). The effect of TKII and CK, fermented *kochujang*, on the NK cell activity of splenocytes was higher than that of sarcoma-180 cells transplanted control group. TK II recovered the activity of hepatic GST that was decreased by the transplantation of sarcoma-180 cells in to the mice. All *kochujang*-treated mice had significantly fewer lung metastatic colonies than control mice. TKII was the most effective in inhibiting lung metastasis of colon 26-M3.1 cells. These results indicated that optimally ripened (6-month) TK had more suppressive effects on tumor formation and lung metastasis than RPP and *kochujang* without fermentation and commercially prepared *kochujang* in mice.

Key words: *kochujang*, sarcoma-180 cells, natural killer cells, glutathione *S*-transferase, metastasis

INTRODUCTION

Kochujang (red pepper soybean paste) is a Korean traditional fermented food, which has been eaten with *doenjang* (soy paste) for a long time in Korea. It has been played an important role in providing specific taste and flavor in foods. The overall savor of *kochujang* is a combination of savory, sweet, pungent and salty flavors, which originates from a fermentation of raw materials such as *kochujang meju*, starch sources, red pepper powder and salt (1-5).

Kochujang can be classified into two groups, traditional *kochujang* using *meju* (by the conventional method) and commercially prepared *kochujang* (by a convenient method) using *koji* or bacterial enzymes. Generally, traditional *kochujang* is prepared with glutinous rice, *meju* (naturally fermented soy paste), red pepper powder and salt, which is fermented for 6 to 18 months by enzymatic reaction of bacteria or yeast. The malt is an optional ingredient that may be used to saccharify glutinous rice. In commercial *kochujang*, soybean and rice *koji* mixture is substituted for *meju*. To prepare *koji*, soy bean and rice are inoculated with *Aspergillus oryzae*, which is incubated at 30°C for 3~4 days, respectively. Commercial *kochujang* has the advantage of reducing fermentation time (15~60 days) in comparison with traditional methods (3).

Kochujang is fermented with red pepper powder and *meju* etc. that are known to have antimutagenic and the anticancer properties (6-13). Several studies indicated that traditional *kochujang* exhibits higher antimutagenic activity than commercially prepared *kochujang*, and the *meju*, *koji* and glutenous rice powder seem to be one of the major antimutagenic components in *kochujang*. It is also suggested that the quality of *kochujang* is influenced by several factors such as ratio of raw material, fermentation time and meshing method (3).

In this study, the effects of *kochujang* prepared with different manufacturing methods and fermentation periods on tumor formation, natural killer (NK) cell activity in spleen and glutathione *S*-transferase (GST) activity in liver were investigated in sarcoma-180 cell transplanted mice. Inhibitory effects of these samples on lung metastasis of colon 26-M3.1 cells were also evaluated in Balb/c mice.

MATERIALS AND METHODS

Samples

Traditional *kochujang* (TK) I, II and red pepper powder (RPP) were obtained from Sunchang traditional *kochujang* village (Moonokrye Food Co., Sunchang, Choenbuk). Commercial *kochujang* (Chungjungwon from Daesang, Co., Sunchang, Cheonbuk) was purchased from local market in Busan, Korea.

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Kochujang samples were freeze dried and powdered, and the RPP was powdered. 20-folds of methanol was added to the powdered samples and extracted by shaking 3 times. The methanol extracts were evaporated using a vacuum evaporator, concentrated, then dissolved in phosphate buffered saline (PBS).

Animals

4 week-old male and 6 week-old female Balb/c mice were supplied by the Korean Chemistry Institute (Taejon, Korea). A basal diet and drinking water were available *ad libitum*. Mice were housed in polycarbonate cages with a 12 hrs light/dark cycle in a temperature (21±2°C) controlled room.

Cell cultures

Yac-1 cells, a NK-sensitive mouse lymphoma cell line were maintained in RPMI-1640 supplemented with 10% FBS. A highly metastatic line of colon 26-M3.1 carcinoma were maintained as monolayer cultures in Eagle's MEM supplemented with 7.5% FBS, vitamin solution, sodium pyruvate, none-essential amino acids and L-glutamine. Cultures were maintained in a humidified atmosphere of 5% CO_2 at 37°C.

Solid tumor formation in mice

7 day-old sarcoma-180 ascites cells were transplanted subcutaneously into the left groin of 4 week-old Balb/c mice at a dose of 6×10^6 cells/mouse. One mg/kg of methanol extracts from TKI, TKII, CK and RPP were injected i.p. once a day for 20 days from 24 hrs after the transplantation. Following 32 days, the formed tumors were dissected and weighed. The inhibition rate was calculated as: Inhibition rate (%) = (Cw-Tw)/Cw × 100, where Cw was the average tumor weight of the control group and Tw was that of sample treated group.

Preparation of cytosolic fraction

Livers were quickly removed, weighed and homogenized in potassium phosphate buffer (pH 7.4), centrifugated at 13,000×g, 4°C for 10 minutes, and the supernatant was centrifugated again at 105,000×g, 4°C for 1 hour to obtain cytosolic upper fraction, which was stored at -72°C.

GST activity

Cytosolic glutathione S-transferase (GST) activities in the liver were measured by the method of Habig et al. (14).

Natural killer cell activity

Isolation of spleen lymphocyte

The spleen was dissected aseptically and ground in RPMI 1640 (GIBCO Co.) supplemented with penicillin (100 U/mL) and streptomycin (100 μg/mL). The cell suspension was filtered through 70 μm nylon mesh, and the lymphocytes were collected by the centrifugation, resuspended in the same media. Lymphocytes were isolated by centrifugation using histopaque-1077 (400 g, 30 min, 18 °C).

NK activity and preparation of effector cells

The assay for NK cell activity (15,16) was adapted from the method of using the dye, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The Yac-1 murine lymphoma cell line was used as target cell. Yac-1 cells were maintained at a density of 2×10^5 cells/mL in RPMI 1640 supplemented with 10% FCS, penicillin (100 U/mL) and streptomycin (100 μg/mL). The cells were collected by centrifugation and resuspended at a concentration of 5×10^4 cells/mL. For the NK cell activity assay, 50μl each of effector cells (2.5×10^6 cells/mL) and Yac-1 cells (5×10^4 cells/mL) were added to each well of a 96 well flat bottomed microtitre plate. The effector/target cells ratio was 50 : 1. After 3 days culture at 37°C, the cells were loaded with 10 μL of freshly prepared MTT (5 mg/mL) and incubated for a further 4 hours at 37°C. Twenty five μL of sodium dodecyl sulfate (SDS, 10% in 0.02 N HCl) was added to each well and were left 30 min at room temperature for color development. The optical density (OD) was measured at a wavelength of 540 nm by ELISA reader. The percentage cell cytolysis was calculated as:

$$\text{Cytolysis (\%)} = \frac{\text{OD of non-lysed target cells} - \text{OD of effector cells}}{\text{OD of target cells alone}} \times 100$$

Experimental lung metastasis

Experimental lung metastasis were assessed by means of colon 26-M3.1 cells injection into the lateral tail vein of 6 week-old female Balb/c mice. The mice were administered with the indicated doses of *kochujang* and RPP by s.c., which were inoculated i.v. with colon 26 M~3.1 (2.5×10^4/mouse) cells after 2 days. The mice were killed 2 weeks later and their lungs were fixed in Bouin's solution (saturated picric acid : formalin : acetic acid=15 : 5 : 1, v/v/v). Lung tumor colonies that metastasized were counted under a dissecting microscope (17).

Statistical analysis

Statistical analysis was performed by analysis of variance. Significant differences between treatment means were determined by using Duncan's multiple range test (18).

RESULTS AND DISCUSSION

Inhibitory effect of *kochujang* on solid tumor formation

To investigate the inhibitory effect of *kochujang* on solid tumor formation in sarcoma-180 cells transplanted mice, 1.0 g/kg of methanol extract from traditional *kochujang* I (TKI, 0-day fermented), II (TKII, 6-month fermented), commercial *kochujang* (CK, 1-month fermented), or red pepper powder (RPP) was employed from the result of the viability test (data not shown). The injection of the *kochujang* and RPP extracts significantly reduced ($p<0.05$) the tumor formation in the Balb/c mice (Table 1). TKI and CK caused 17% and 23% inhibition of tumor formation, respectively.

Table 1. Antitumor activities of methanol extracts from various kinds of *kochujang* and red pepper powder (RPP) in tumor bearing Balb/c mouse with sarcoma-180 cells[1)]

Sample	Tumor wt. (g)	Inhibition rate (%)
S-180+PBS	$6.0\pm0.1^{a6)}$	-
S-180+CK[2)]	4.5 ± 0.1^{bc}	23
S-180+TK I [3)]	5.0 ± 0.9^{ab}	17
S-180+TK II[4)]	3.3 ± 0.3^{c}	45
S-180+RPP[5)]	4.7 ± 0.3^{b}	22

[1)]7-days sarcoma-180 ascites cells were s.c. transplanted into the left groin of inbredstrain. 1.0 mg/kg of methanol extract from various kinds of *kochujang*, red pepper powder or the equal volume of phosphate buffered saline (control) was i.p. injected once a day for 20 days from 24 hr following transplantation. All mice were sacrificed at 5 weeks following the transplantation, and tumor, spleen and liver weight were measured.
[2)]Commercial *kochujang*: Daesang Co.
[3)]Traditional *kochujang* I: 0 day fermented *kochujang*, Moonokrye Co.
[4)]Traditional *kochujang* II: 6 month fermented *kochujang*, Moonokrye Co.
[5)]RPP: the same as added in TKI and II
[6)]Means with the different letters are significantly different ($p<0.05$) by Duncan's multiple range test.

Especially, TKII decreased tumor growth by 46% compared with control, resulting in the smallest tumor weight. These results indicate that antitumor activity of optimally ripened TK was stronger than that of CK or TK without fermentation.

It has already been reported that the methanol extracts of traditional *kochujang* showed higher antimutagenic activities than those of commercial one against AFB_1 and MNNG in Ames test using *Salmonella typhimurium* TA100, and MNNG in SOS chromotest using *E. coli* PQ37 (19,20). Jung et al. (21) also reported that *kochujang* had an inhibitory effect similar to *doenjang* on the mutagenicity induced by AFB_1 in *Salmonella typhimurium* TA98 and homemade *kochujang* had higher antimutagenicity than commercial *kochujang*. These data suggested that TK had higher *in vitro* antimutagenic and *in vivo* antitumor effects than CK.

Body weights and index of spleen and liver

The body weight of all sarcoma-180 cells transplanted groups was significantly higher ($p<0.05$) than that of normal group (Table 2, $p<0.05$). The injection of sarcoma-180 cells increased the spleen/body weight ratio of Balb/c mice, while TKI and TKII decreased this index ($p<0.05$). There was no significant difference on the liver/body weight ratio among the experimental groups.

Table 2. Effects of methanol extracts from various kinds of *kochujang* and red pepper powder (RPP) on the body weights and spleen and liver index in sarcoma-180 cells[1)] transplanted Balb/c mouse

Sample	Body wt. (g)	Spleen/body wt. (%)	Liver/body wt. (%)
Control (normal)	$23.9\pm1.4^{a6)}$	0.4 ± 0.0^{c}	$6.1\pm1.7^{ns7)}$
S-180+PBS	27.3 ± 1.5^{b}	0.9 ± 0.1^{ab}	6.5 ± 1.4
S-180+CK[2)]	26.4 ± 1.1^{b}	0.8 ± 0.2^{ab}	6.9 ± 0.7
S-180+TKI[3)]	27.8 ± 1.5^{b}	0.7 ± 0.1^{b}	7.0 ± 1.5
S-180+TKII[4)]	26.4 ± 2.0^{b}	0.7 ± 0.1^{b}	7.1 ± 1.7
S-180+RPP[5)]	26.8 ± 2.0^{b}	1.0 ± 0.2^{a}	6.6 ± 1.1

[1)~5)]The explanation is the same as shown in Table 1.
[6)]Means with the different letters are significantly different ($p<0.05$) by Duncan's multiple range test.
[7)]not significant

NK cell activity in the spleen

Natural killer (NK) cells are a subset of cytotoxic lymphocytes found mainly in blood and the spleen. NK cells play a role in providing a natural immunity to microbes, viruses and tumor cells and are involved in the rejection of grafts (22). An NK cell deficiency can result in higher susceptibility to neoplastic growth (23).

To study the function of *kochujang* in the immune system of sarcoma-180 cells transplanted mice, the NK cell activity of splenocytes was measured, using Yac-1 murine lymphoma cell line as target cell. At a lymphocyte/target cell ratio of 50 : 1, the NK cell activity of sarcoma-180 cells treated group significantly ($p<0.05$) decreased compared to the normal group (Fig. 1). The effects of TKII and CK, fermented *kochujang*, on the NK cell activity of splenocyte were higher than that of sarcoma-180 cells transplanted control group. Especially, TKII enhanced the NK cell activity of splenocyte by 1.8 times compared to sarcoma-180 cells transplanted control group, showing the highest NK cell activity.

GST activity in the liver

Glutathione *S*-transferase (GST) plays an important role in the detoxification of many hydrophobic compounds bearing an electrophilic center by the conjugation with the thiol

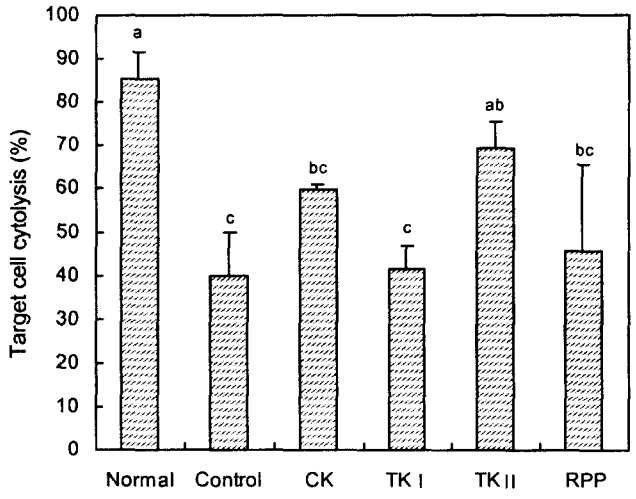

Fig. 1. Effects of methanol extracts from various kinds of *kochujang* and red pepper powder sample on natural killer (NK) cell activity of splenic lympocytes in normal and sarcoma-180 cells transplanted Balb/c mice. The Yac-1 murine lymphoma cell line was used as target cells. The effector/target cells ratio was 50 : 1. CK; Commercial *kochujang*: Daesang Co. TK; Traditional *kochujang* I: 0 day fermented *kochujang*, Moonokrye Co. TKII; Traditional *kochujang* II: 6 month fermented *kochujang*, Moonokrye Co. RPP; Red pepper powder: the same as added in TKI and II.
[a~c]Means with the different letters are significantly different ($p<0.05$) by Duncan's multiple range test.

group of glutathione (24,25).

Hepatic GST activity in the sarcoma-180 cells transplanted mice decreased to 722 nmol/mg protein/min compared to the normal group's activity of 842 nmol/mg protein/min (Fig. 2). TKII recovered the activity of hepatic GST to 776 nmol/mg protein/min in sarcoma-180 cells transplanted mice.

From these results, the transplantation of the tumor cells in the mice decreased the hepatic GST activity, while the fermented traditional *kochujang* (TKII) seemed to recover this detoxifying enzyme in the liver.

From the results of the above experiments, it might be concluded that TKII was the most effective in preventing cancer by decreasing tumor formation and increasing the NK cell activity in spleen and GST activity in the liver of the mice.

Experimental lung metastasis

It is well known that the most deaths caused by cancer are not the result of primary tumor growth but, rather, are due to the dissemination of tumor cells to secondary sites by a series of events known collectively as the metastatic cascade (26).

In this experiment, we investigated antitumor activity of *kochujang* extracts with respect to the prophylactic inhibition of tumor metastasis using a experimental metastasis model in mice (Table 3). All *kochujang*-treated mice had significantly fewer lung metastatic colonies than the control mice. TKII was the most effective in inhibiting lung metastasis of colon 26-M3.1 cells.

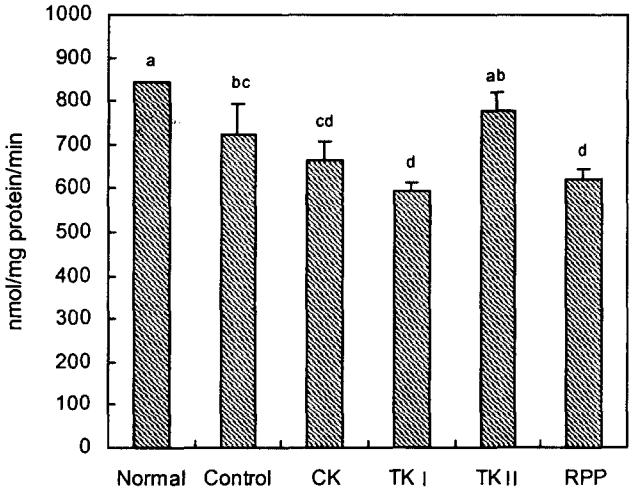

Fig. 2. The effects of various kinds of *kochujang* and red pepper powder sample on the activity of hepatic glutathione *S*-transferase in normal and sarcoma-180 cells transplanted Balb/c mice. CK; Commercial *kochujang*: Daesang Co. TKI; Traditional *kochujang* I: 0 day fermented *kochujang*, Moonokrye Co. TKII; Traditional *kochujang* II: 6 month fermented *kochujang*, Moonokrye Co. RPP; Red pepper powder: the same as added in TKI and II.
[a~d]Means with the different letters are significantly different ($p<0.05$) by Duncan's multiple range test.

Table 3. Inhibitory effect of methanol extracts from various kinds of *kochujang* and red pepper powder (RPP) on tumor metastasis produced by colon 26-M3.1 cells in Balb/c mice

Treatment	Dose (mg/mouse)	Route	No. of lung metastasis (Inhibition, %) Mean ± SD	Range
Control		sc	318 ± 11^{a}	310~330
CK[1]	0.25	sc	208 ± 56^{ab} (34)	163~271
	1.25	sc	133 ± 15^{c} (58)	124~150
TKI[2]	0.25	sc	121 ± 105^{bc} (62)	90~260
	1.25	sc	165 ± 87^{bc} (48)	60~242
TKII[3]	0.25	sc	52 ± 63^{c} (48)	4~123
	1.25	sc	66 ± 88^{c} (84)	3~166
RPP[4]	0.25	sc	308 ± 12^{a} (3)	297~321
	1.25	sc	258 ± 34^{ab} (19)	233~296

[1]Commercial *kochujang*: Daesang Co.
[2]Traditional *kochujang* I: 0 day fermented *kochujang*, Moonokrye Co.
[3]Traditional *kochujang* II: 6 month fermented *kochujang*, Moonokrye Co.
[4]Red pepper powder: the same as added in TKI and II
[5]Means with the different letters are significantly different ($p<0.05$) by Duncan's multiple range test

Therefore, it is considered that the optimally ripened (6-month) TK had more suppressive effects on tumor formation and lung metastasis than RPP, CK and TK without fermentation. Several studies indicated that fermented foods revealed the difference of antimutagenic and anticarcinogenic activities according to the fermentation periods (27-30). It is reported that fermented *doenjang* or *chungkookjang* showed higher antimutagenic effect than non-fermented cooked soybean (27,28). Korean cabbage *kimchi* exhibited the highest antimutagenic and anticarcinogenic effect on optimally ripened *kimchi* (29,30). As demonstrated in other fermented foods, *in vivo* antitumor effects of optimally fermented TK were higher than TK without fermentaion. It seems that the high inhibition rate in fermented TK probably results from some end products produced by the action of microorganisms during fermentation of *kochujang*. Further study is needed to identify components and mechanisms for the differences of activity between traditional *kochujang* and commercial *kochujang*.

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