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The Effect of *Doenjang* (Korean Soy Paste) on the Liver Enzyme Activities of the Sarcoma-180 Cell Transplanted Mice

Moon-Kyung Kim, Suk-Hee Moon*, Jong-Won Choi and Kun-Young Park†**

Department of Food Science and Nutrition, and Pusan Cancer Research Center, Pusan National University, Pusan 609-735, Korea
**Department of Food and Nutrition, Kyungnam College of Information & Technology, Pusan 616-701, Korea*
***College of Pharmacy, Kyungsung University, Pusan 608-736, Korea*

Abstract

Korean traditional fermented soy paste (*doenjang*) prolonged the life span of Balb/c mice injected with the sarcoma-180 cells. The activities of liver enzymes, such as xanthine oxidase, aminopyrine N-demethylase, aniline hydroxylase, γ-glutamylcysteine synthetase, glutathione reductase and glutathione S-transferase (GST), and the contents of lipid peroxide and glutathione were determined from the sarcoma-180 cell injected mice that were treated with methanol extracts from *doenjang*, *miso* and soybean. The content of lipid peroxide and the activity of xanthine oxidase in the liver of Balb/c mice which were increased by the transplantation of the sarcoma-180 cells were decreased by treatment with the methanol extract from *doenjang*. But the activities of aminopyrine N-demethylase and aniline hydroxylase were not affected by the treatment of methanol extracts from *doenjang* to the mice injected with the sarcoma-180 cells. The content of glutathione, the activities of glutamylcysteine synthetase, glutathione reductase and glutathione S-transferase decreased by the injection of the sarcoma-180 were recovered considerably by the treatment of the methanol extract from *doenjang*.

Key words: *doenjang*, sarcoma-180 cell, glutathione content, liver enzyme activities

INTRODUCTION

Fermented foods are an important part of the diet of people in some areas of the world. For example, *doenjang* (fermented soy paste) is one of the most important fermented foods in Korea.

Many studies reported that good components of soybean, especially the trypsin inhibitor, isoflavone, phytic acid, saponin, lignin, vitamin E and unsaturated fatty acids protected against the carcinogenesis, significantly (1-5). Isoflavones present in soybean, genistein, daidzein and glycitein have been reported to have anticarcinogenic, antifungal, and antioxidant properties (6-8). In particular, genistein might be a promising chemopreventive agent due to its capability to modulate the cellular detoxification enzyme (9). Daidzein has also been reported to inhibit human breast cancer cells and antiestrogenic activity (6,10). Barnes (7) reported that the presence of soybeans in the diet caused chemoprevention in rat models of breast cancer, and the active substances in soybeans were the phytoestrogens, potentially acting as inhibitors of estrogen action or modulators of hepatic metabolism. Son (11) reported that the solid tumor growth of the Balb/c mice injected with sarcoma-180 cells was inhibited and the life span, spleen index and phagocytic activity of the mice were increased when commercial *doenjang* extracts were administered. Mirsalis et al. (12) reported that soybean extracts elevated the activities of glutathione S-transferase, UDP-glucuronosyltransferase and the detoxification enzymes of chemical carcinogenic compounds. And Son (11) also reported that the content of lipid peroxide and the activity of xanthine oxidase increased by the injection of sarcoma-180 cells were decreased considerably after the treatment of commercial *doenjang* extracts. Whereas, the glutathione content, the activities of glutathione S-transferase, glutamylcysteine synthetase and glutathione reductase which were associated with the detoxification system were decreased by the sarcoma-180 cells injection, but those were increased by the treatment of commercial *doenjang* extract.

In this paper the rate of life span elongation was measured when the methanol extracts from traditionally made *doenjang*, *miso* (Japanese soy paste) and cooked soybean were treated to the sarcoma-180 cells injected Balb/c mice. And the changes in the activities of hepatic enzymes, such as xanthine oxidase, aminopyrine N-demethylase, aniline hydroxylase, γ-glutamylcysteine synthetase, glutathione reductase and glutathione S-transferase, and in the contents of lipid peroxide and glutathione, which are associated with toxic and detoxification systems, were studied.

MATERIALS AND METHODS

Materials

Korean traditional *doenjang* was made from Jangyeob soybean. The dried *mejues* were fermented for 3 months. Salt and water were added to the fermented *mejues*. The paste was separated from the mixture and then ripened and used as a *doenjang* sample. *Miso* (soybean : rice : salt = 100 : 60 : 40, Maruseng Co., Japan) was purchased from a local market

†Corresponding author. E-mail: kunypark@hyown.pusan.ac.kr
Phone: 82-51-510-2839, Fax: 82-51-514-3138

in Pusan. The variety of Jangyeob soybean was cooked (autoclaved) and used as a soybean sample.

Preparation of methanol extract

The *doenjang*, *miso* and soybean were freeze dried and powdered. The powders were extracted in methanol (1:10, g/v) for 8 hrs by three times. The methanol extract was dried by using a vacuum evaporator (Buchi RE121, Switzerland) and then trasferred to vials, and dissolved in DMSO (dimethylsulfoxide) for the test.

Animals

Male Balb/c mice at 4 weeks of age were used in this experiment. A basal diet and drinking water were available *ad libitum*. The temperature and relative humidity were 21±2°C and 55±5%, respectively, and a 12 hr light/dark cycle was maintained.

Survival test

Male Balb/c mice were injected i.p. with 1 ml (1×10^6 cells/mouse) of 7 day-old sarcoma-180 ascites cells. After 24 hrs following transplantation, methanol extracts from the *doenjang*, *miso* and soybean were injected i.p. once a day for 20 days and survival times of the mice were recorded.

Preparation of liver homogenates, microsomal and cytosol fractions

7 day-old sarcoma-180 ascites cells were transplanted subcutanously into the left groin of Balb/c mice at a dose of 6×10^6 cells/mouse. 0.1 mg/kg of methanol extracts from the *doenjang*, *miso*, soybean and the equal volume of phosphate buffered solution (control) was injected i.p. once a day for 20 days from 24 hrs following transplantation. All mice were sacrificed at 5 weeks following the transplantation. Livers were quickly removed, weighed and homogenized in 0.25 M sucrose buffer containing 2 mM-mercaptoethanol (1.4, g/v) using a glass teflon homogenizer. The homogenate was centrifuged at 600×g for 10 min, the supernatant was further centrifuged at 10,000×g for 20 min. And then the supernatant was centrifuged again at 105,000×g for 60 min to obtain upper fraction as cytosol and lower microsomal fraction. The microsome was resuspended in the same volume of 0.25 M sucrose buffer and contrifuged at 105,000×g for 60 min to obtain the microsomal fraction. The homogenate, microsomal fraction and cytosol fraction were used for the determination of the content of lipid peroxide and glutathione, and the activities of xanthine oxidase, aminopyrine N-demethylase, aniline hydroxylase, glutathione S-transferase, γ-glutamylcysteine synthetase and glutathione reductase.

Enzyme assays

The content of lipid peroxide was determined by the method of Ohkawa et al. (13). The activity of xanthine oxidase was measured by the method of Stripe and Della (14). Enzyme activity was defined as *n* mole uric acid formed per mg protein per min at 30°C. The glutathione contents and glutahione S-transferase activity were determined by the method of Ellaman (15) and Habig et al. (16), respectively. The activities of aminopyrine N-demethylase, aniline hydroxylase, γ-glutamylcysteine synthetase and glutathione reductase were measured using the method of Nash (17), Bidlack and Lowery (18), Meister and Richman (19) and Mize and Longdon (20), respectively.

Statistical analysis

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

RESULTS AND DISCUSSION

After the methanol extracts from *doenjang*, *miso* and soybean were treated to the mice injected with the sarcoma-180 cells, the survival time was recorded. Table 1 showed that the *doenjang* treated group (47.7 days) lived the longest ($p<0.05$) among the control group (28.4 days), soybean treated group (31.4 days) and *miso* treated group (40.1 days). The effects of the methanol extracts from *doenjang*, *miso* and soybean on the changes of some serum and liver enzyme activity in sarcoma-180 transplanted mice were studied. The solid tumor growth was inhibited when 0.1 mg/kg of *doenjang*, *miso* or soybean extracts, esperially *doenjang* was administrated to the Balb/c mice (data not shown).

The effects of the methanol extracts from *doenjang*, *miso* and soybean on the lipid peroxide content were demonstrated in Fig. 1. The injection of the sarcoma-180 cells increased lipid peroxide content to 51.5 malondialdehyde n mol/g from a control value of 26.8 malondialdehyde n mol/g. But lipid peroxide contents markedly were decreased by the treatment of the methanol extract from *miso* and soybean, especially, *doenjang* to a value of 35.9 malondialdehyde n mol/g.

It has been observed that the xanthine oxidase activities in both the serum and liver were increased with liver damage such as viral hepatitis and bacterial infection (21). Even in liver damage induced by biological toxin (*Streptococcus* toxin) and xenobiotics (carbon tetrachloride), xanthine oxidase activities in the liver or serum have been demonstrated to be elevated in an animal model (22). Interestingly, in a study

Table 1. The effect of methanol extracts of *doenjang*, *miso* and soybean on the life span of Balb/c mice with the sarcoma-180 cells

Treatment	Survival time (day)	Prolongation rate (%)
Control+S-180	28.4 ± 1.9^{a}	
Doenjang+S-180	47.7 ± 4.6^{c}	68
Miso+S-180	40.1 ± 3.4^{bc}	41
Soybean+S-180	31.4 ± 8.2^{ab}	11

7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and the equal volume of phosphate buffered solution (control) was i.p. injected once a day for 20 days from 24 hr following transplantation.

$^{a-c}$Means with different letters beside symbols are significantly different at the 0.05 level of significance as determined by Duncan's multiple range test.

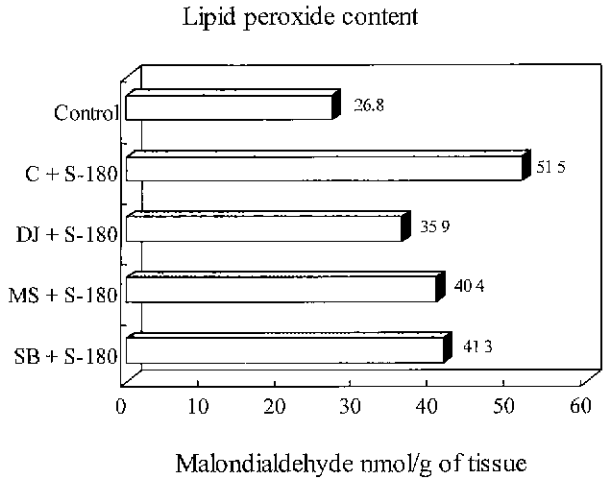

Fig. 1. The effect of methanol extracts from *doenjang* (DJ), *miso* (MS) and soybean (SB) on lipid peroxide content in sarcoma-180 treated Balb/c mice. 7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and an equal volume of phosphate buffered solution (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 the lipid peroxide content was measured.

by Tubaro et al. (23), direct administration of liver xanthine oxidase to mice with bacterial infections resulted in a significant decrease in mortality rate. The present experiment herein also showed that injection of the sarcoma-180 cells in the mice increased the activity of hepatic xanthine oxidase (Fig. 2). This activity was inhibited by the methanol extract from *doenjang*, but the methanol extracts from *miso* and soybean did not show any such inhibitory effect.

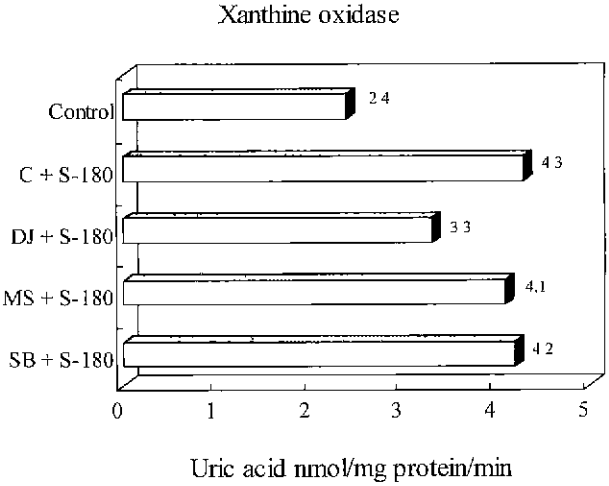

Fig. 2. The effect of methanol extracts from *doenjang* (DJ), *miso* (MS) and soybean (SB) on hepatic xanthine oxidase in sarcoma-180 treated Balb/c mice. 7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and an equal volume of phosphate buffered solution (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 the enzyme activity of the liver was measured

Xenobiotics were detoxified or inactivated by the metabolizing enzyme system of the liver smooth endoplasmic reticulum and then eliminated (21). Phase I enzyme, the cytochrome P-450 mixed function oxidase, participates in this process and is divided into type I and type II reactions based on drug binding type and site existence (22). Type I and type II catalyze aminopyrine and aniline as a substrate, and produce formaldehyde and *p*-aminophenol as a product, respectively, which is associated with the production of free radicals in the microsomal system (22,23). Phase I enzymes introduce polar groups into xenobiotic compounds, and the presence of a polar group on a xenobiotic compound provides a means by which a subsequent conjugation by a phase II enzyme (GST, UDP-glucuronosyltransferase) reaction can occur, leading to excretion (24,25). Table 2 presents the changes in the activities of hepatic aminopyrine N-demethylase and aniline hydroxylase. The injection of the sarcoma-180 cells did not increase the activity of aminopyrine N-demethylase compared with the control. There was no inhibition of the enzyme activity by the treatment of the methanol extracts from *doenjang*, *miso* and soybean. There was no changes of aniline hydroxylase activity following the sarcoma-180 cells injection compared with the control. The activity of aniline hydroxylase after the treatment of the methanol extracts from *doenjang*, *miso* and soybean was not changed by the injection of the sarcoma-180 cells.

The change of glutathione reductase activity was studied to elucidate the change of the glutathione content (Fig. 3). The glutathione reductase activity by the injection of the sarcoma-180 cells decreased to 44.8 nmoles/mg protein from a control value of 65.3 nmoles/mg protein. But those activities were recovered by the treatment of the methanol extracts from *miso* and soybean, and especially, *doenjang*.

Glutathione, a tripeptide containing a sulfhydryl group, is a highly distinctive amino acid derivative with several important roles. For example, glutathione protects red cells from oxidative damage and plays a key role in detoxification by reacting with hydrogen peroxide, organic peroxides, and the

Table 2. The effect of methanol extracts from *doenjang*, *miso* and soybean on the activities of hepatic aminopyrine N-demethylase and aniline hydroxylase in sarcoma-180 treated Balb/c mice

Treatment	Enzyme activity	
	Formaldehyde nmol/mg protein/min	*p*-Aminophenol nmol/mg protein/min
Control	3.16±0.33	0.48±0.03
Control+S-180	3.35±0.26	0.47±0.03
Donejang+S-180	3.28±0.40	0.48±0.02
Miso+S-180	3.30±0.31	0.47±0.02
Soybean+S-180	3.11±0.24	0.48±0.02

7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and an equal volume of phosphate buffered solution (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 the enzyme activity of the liver was measured.

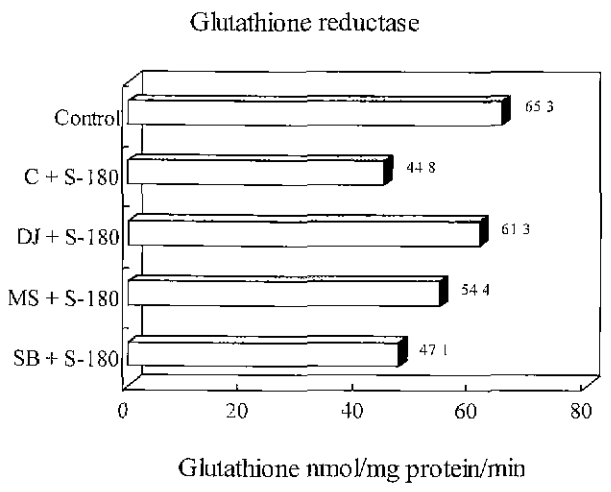

Fig. 3. The effect of methanol extracts from *doenjang* (DJ), *miso* (MS) and soybean (SB) on hepatic glutathione reductase in sarcoma-180 treated Balb/c mice. 7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and an equal volume of phosphate buffered solution (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 the enzyme activity of the liver was measured.

harmful by-products of aerobic life (26). Fig. 4 presents the changes of hepatic glutathione content when the methanol extracts from *doenjang*, *miso* and soybean were injected to the mice treated with sarcoma-180 cells. The hepatic glutathione content after the sarcoma-180 cells treatment was markedly decreased compared to the control, but this level was increased by the treatment of the methanol extract from *doenjang*. Whereas, there was no recovery effect by the treatment

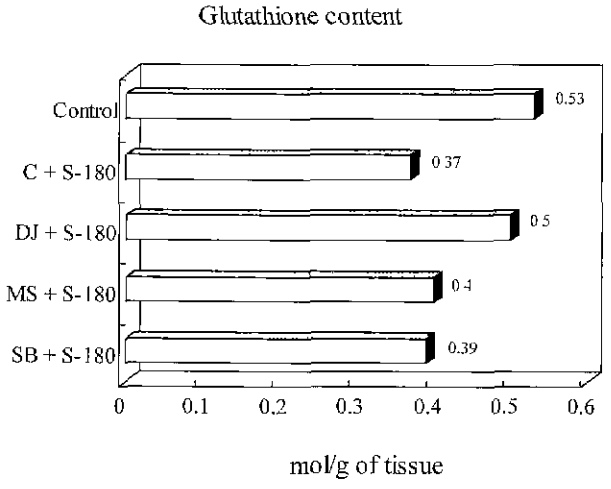

Fig. 4. The effect of methanol extracts from *doenjang* (DJ), *miso* (MS) and soybean (SB) on the hepatic glutathione content in sarcoma-180 treated Balb/c mice. 7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and an equal volume of phosphate buffered solution (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 the enzyme activity of the liver was measured.

of the methanol extracts from *miso* and soybean.

Table 3 presents the changes of γ-glutamylcysteine synthetase activity which participates in glutathione synthesis. The injection of the sarcoma-180 cells decreased the activity of γ-glutamylcysteine synthetase compared to the control. This activity was recovered following the treatment of the methanol extract from *doenjang*. *Miso* and soybean extracts did not appear to effect the activity of γ-glutamylcysteine synthetase.

It has been suggested that the chemoprotective action of anticarcinogenic compounds may be due to elevation of detoxification enzymes (27,28). An important drug-metabolizing or detoxification enzyme is glutathione S-transferase (GST). GST catalyzes the reaction of a wide variety of electrophiles with glutathione (GSH). Since most of the chemical carcinogens are electrophiles, GST takes on considerable importance in carcinogen inactivation (24,25). A number of studies have been carried out on compounds that inhibit carcinogenesis by increasing GST. For example, butylated hydroxyanisole, a food additive, has been found to protect against chemical carcinogenesis, and to increase the levels of liver microsomal epoxide hydratase, GST and glutathione (29). Fig. 5 presents the changes in the activity of hepatic cytosolic glutathione S-transferase (GST). The injection of the sarcoma-180 cells decreased GST activity to 289.4 nmoles/mg protein from a control value of 342.6 nmoles/mg protein. But the activity was somewhat recovered by the treatment of the methanol extracts from *doenjang* and *miso*. The above recovered activity of GST may result from the detoxification of the toxic metabolites. But the activity of GST was not affected by the treatment of the methanol extract from soybean.

According to Kim's data, *doenjang* has more anticancer effects than *miso* and soybean by inhibiting the growth of human cancer cells and the formation of tumors to the Balb/c mice injected with the sarcoma-180 cells (30). In conclusion, *doenjang* demonstrated that it exerted more anticancer effects than *miso* and soybean, controlling the activities of the liver enzymes which were associated with the detoxification mechanism.

Table 3. The effect of methanol extracts from *doenjang*, *miso* and soybean on hepatic γ-glutamylcysteine synthetase activity in sarcoma-180 treated Balb/c mice

Treatment	Enzyme activity
	Pi formed nmol/mg protein/min
Control	7.21±0.97
Control+S-180	6.52±0.52
Donejang+S-180	7.22±0.98
Miso+S-180	5.82±0.48
Soybean+S-180	6.52±0.53

7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and an equal volume of phosphate buffered solution (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 the enzyme activity of the liver was measured.

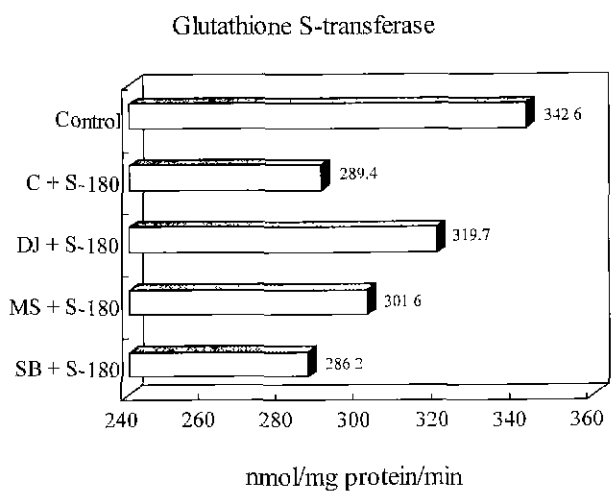

Fig. 5. The effect of methanol extracts from *doenjang* (DJ), *miso* (MS) and soybean (SB) on hepatic glutathione-S-transferase in sarcoma-180 treated Balb/c mice. 7 day-old sarcoma-180 cells were S.C. transplanted into the left groin of the inbred strain. 0.1 mg/kg of methanol extracts from *doenjang*, *miso*, soybean and an equal volume of phosphate buffered solution (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 the glutathione content was measured.

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