CANCER
PREVENTION RESEARCH

□ ORIGINAL ARTICLE □

Saengshik Administration Reduced the Side Effects of Chemotherapy in Chemotherapeutic Agent Injected Mice

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Chemotherapy is a method to treat cancer by destroying cancer cells, and the effectiveness of agents on various types of cancer cells has been confirmed experimentally and clinically. Chemotherapeutic agents cause a range of side effects, mainly affecting the fast-dividing cells of the body. In this study, we explored the alleviative effects of *Saengshik* on the side effects of chemotherapeutic agents, 5-fluorouracil (5-FU) and cisplatin, after single or multiple-dose administration of the agents in mice. The results showed that *Saengshik* had effects against decreasing spleen weight as well as reductions of RBCs, WBCs, and platelets counts. We also observed the effects of *Saengshik* administration against the hepatotoxicity caused by 5-FU and cisplatin, where the preventive effects of *Saengshik* administration on glutamic pyruvic transaminase (GPT) levels were observed. Furthermore, survival time extension was observed after *Saengshik* administration, where the survival rate was prolonged up to 90% in both the *Saengshik* plus 5-FU administered group and the *Saengshik* plus cisplatin administered group. In conclusion, *Saengshik* proved to have alleviative effects on the side-effects of anti-cancer agents. **(*Cancer Prev Res* 12, 319-328, 2007)**

Key Words: Chemotherapeutic agent, Fluorouracil, Cisplatin, Side-Effect, *Saengshik*

INTRODUCTION

A major advantage of chemotherapy is its ability to treat cancer, whereas surgery and radiation therapies are limited to treating cancers that are confined to a specific area. Many common chemotherapeutic agents are limited due to their side effects such as nausea and vomiting, depression of the immune system, anemia, leucopenia, hemorrhage, diarrhea and constipation, malnutrition, appetite and weight loss, hair loss, secondary neoplasms, cardiotoxicity, hepatotoxicity, nephrotoxicity, ototoxicity, and death.[1,2] The drugs lack adequate specificity for tumor cells and can cause significant damage to host tissues. Also, these drugs are most toxic to the rapidly proliferating cells of the blood-forming hematopoietic system, the gastrointestinal tract and hair cells.[3,4] As a result of these toxicities, patients suffer from significant treatment complications, and the dosage of the chemotherapeutic agents must be reduced. Virtually all chemotherapeutic regimens can cause depression of the immune system, often by paralyzing the bone marrow and leading to decreases in white blood cells, red blood cells, and platelets.

Most chemotherapeutic agents and medications work by interfering with DNA synthesis or function, and each chemotherapy drug works during different phases of the cell cycle. 5-Fluorouracil (5-FU) is one of the oldest chemotherapy drugs, and works by interfering with the nucleotide components of DNA to stop DNA synthesis. 5-FU is known as a myelosuppressive cytostatic agent and more strongly affects cells with a high level of proliferating activity, including

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hematopoietic progenitor cells.[5] The platinum analogue Cisplatin (cisplatinum or Cis-diamine-dichloro-platinum; CDDP) is a platinum-based chemotherapy drug that helps in treating cancer by impairing DNA synthesis, transcription, and function, and it acts during any part of the cell cycle.

To relieve the side effects of chemotherapeutic agents, a variety of medicines have been developed, including drugs for nausea and anodynia. Recently, various biological response modifiers have been investigated for the treatment of cancer by immunotherapy, and for the relief of chemotherapy side effects. One of the hematopoietic growth factors, erythropoietin (EPO), which is FDA-approved for the treatment of renal anemia, has also been used to treat anemia caused by chemotherapy.[6,7] Myeloid growth factors [granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulation factor (GM-CSF)] enhance the functions of mature granulocytes and monocytes, thus enhancing defense mechanisms in patients receiving intensive cancer chemotherapy.[3,9] However, they can not be applied to leukemia patients, and to patients with diseases of the heart, kidney, liver, or lungs, or those with sickle cell disease. Chung et al. and Rha et al. reported side effects of GM-CSF such as fever, nausea, chest discomfort and paresthesia.[10,11]

Another means for finding relief from cancer chemotherapy side effects is complementary medicine and dietary supplements, such as vitamins,[12~15] herbs,[16~18] massage[19] and acupuncture.[20,21] Also, many experiments using oriental herbal formulations have been performed to alleviate the side effects of chemotherapeutic agents, and to enhance chemotherapy treatment.[22~26]

Saengshik, a formulated health food, is basically an 'uncooked whole food' that has become popular in Korea, and is reported as being helpful to human health. The ingredients in commercial *Saengshik* include over 40 kinds of vegetative raw materials such as whole grains, vegetables, fruits, mushrooms, and marine plants, as well as various functional botanicals.[27,28] Commercial *Saengshik* products are typically manufactured by freeze-drying or low temperature drying, to avoid nutrient losses by heat treatment, and are then ground into a powder. It can be eaten by emptying an envelope of powder into water, milk, or juice, and then simply drinking it. Various reports exist about the functional effects of *Saengshik*. It has been shown to improve hepatotoxicity, lipid metabolism, and blood glucose, which are often causes of chronic disease.[28~32] Saengshik also has health promoting effects such as for improvements of body strength, anti-obesity, and beauty.[33~35] Previously, there were many attempts to evaluate the effects of *Saengshik* in patients,[36,37] which indicated that *Saengshik* has functional effects and could prevent various diseases.

Accumulating evidence from population-based and laboratory studies supports the association between the regular consumption of fruits, vegetables, and *Saengshik*, and a reduced risk of certain cancers.[38~40] Also, many reports have supported that functional plant materials have interactions with chemotherapy drugs and improve immune function,[12~20,32,41].

The results of prospective studies have given insight into the possible benefits of *Saengshik* consumption in relation to the side effects of chemotherapeutic agents. In this study, we evaluated the alleviative effects of *Saengshik* on the side effects of chemotherapy, including hematotoxicity and hepatotoxicity.

MATERIALS AND METHODS

1. Preparation of the *Saengshik* diet

An AIN93-based diet containing 30% *Saengshik* was prepared by mixing with the *Saengshik* (Erom Co., Ltd, Korea). The *Saengshik* formulation is shown in Table 1. The AIN93 purified diet and 30% *Saengshik* diet compositions are shown in Table 2. The components of the AIN93 diet were purchased from Dyets Inc. (Bethehem, USA). Each diet provided equal energy.

Table 1. Raw materials of *Saengshik*

Materials	
Brown rice	Lotus root
Glutinous millet	Spinach
Sorghum	Chlorella
Prosomillet	*Lentinus edodes*
Soybean	Mugwort
Black sesame	Pine needle
Black rice	Laver
Barley	Brown seaweed
Kale	Sea tangle
Carrot	Yeast
Burdock	*Bifidobacterium longum*
Pumpkin	Fructooligosaccharide
Angelica utills	Lactoferrin
Cabbage	Rose petal extract

Table 2. Comnposition of experimental diet with *Saengshik*

Ingredient	Control diet (%)	30% *Saengshik* diet (%)
Casein	20	14
Corn starch	39.7	27.8
Dyetrose	13.2	9.2
Sucrose	10	7
Cellulose	5	3.5
Soybean oil	7	4.9
AIN93 mineral mixture[1)]	3.5	2.45
AIN93 vitamin Mixture[2)]	1	0.7
L-cystine	0.3	0.2
Choline bitatrate	0.25	0.17
TBHQ	0.0014	0.0014
Total	100	100

[1)]AIN93G mineral mix. (g/kg of mix): calcium carbonate, potassium phosphate monobasic 196, potassium citrate monohydrate 70.78, sodium chloride 74.00, potassium sulfate 46.6, magnesium oxide 24, ferric citrate 6.06, zinc carbonate 1.65, manganese carbonate 0.63, copper carbonate 0.3, potassium sulfatei · $12H_2O$ 0.275, ammonium paramolybdate · $4H_2O$ 0.00795, sodium metasilicate · $9H_2O$ 1.45, chromium potassium sulfate · $12H_2O$ 0.275, ammonium vanadate 0.0066, lithium chloride 0.0174, boric acid 0.08145, sodium fluoride 0.0635, nickel carbonate 0.0318, powdered sucrose 221.026. [2)]AIN93G vitamin mix. (g/kg of mix): nicotinic acid 3.0, Ca pantothenate 1.6, pyridoxine-HCl 0.7, thiamin-HCl 0.6, riboflavin 0.6, folic acid 0.2, biotin 0.02, vitamin B12 (0.1% in mannitol) 2.5, vitamin E (500 IU/g) 15.0, vitamin A (500,000 IU/g) 0.8, vitamin D3 (400,000 IU/g) 0.25, vitamin K1 (phylloquinone) 0.075, powdered sucrose 974.655.

2. Animals

Four-week-old male C57/BL6 mice (Daehan biolink Co. Ltd., Korea) were normalized for 1 week and then randomly divided into each diet group. The groups constituted 10 animals each, and were treated with the therapeutic agents intraperitoneally. All the mice were housed in plastic cages with wire tops and sawdust bedding with a 12 h light-dark cycle and were allowed free access to water.

3. Experimental Design

1) Single-dose administration experiment: The groups were divided into control, 5-FU, and 5-FU+*Saengshik* groups. For 2 weeks the control and 5-FU groups were fed the AIN93 purified diet, while the 5-FU+*Saengshik* group was fed the 30% *Saengshik* diet. The 5-FU and 5-FU+*Saengshik* groups were injected with 200 mg/kg of 5-FU intrapeneally after one week of diet administration, and the diet was then fed an additional week. The 5-FU was purchased from Sigma Chemical Co. (USA).

2) Multiple-dose administration experiment: The mice were divided into a control group, chemotherapeutic agent 5-FU group, cisplatin (Sigma) group, 5-FU+*Saengshik* group, and cisplatin+*Saengshik* group. The *Saengshik* was administered for 3 weeks and the 5-FU (50 mg/kg) or cisplatin (10 mg/kg) were injected 3 times at 2 day intervals, and then the *Saengshik* was fed one more week.

4. Hematologic examinations

Whole blood cells were collected from the hearts of the mice following cervical dislocation and stored in collection tubes containing K_3EDTA (BD Vacutainer Systems. UK). The fluctuations in the hematograms were automatically counted by an automatic blood cell counter (Medonic 620 Hematology analyzer, Clinical Diagnostic Solutions, Inc, USA).

5. Serum GPT level

Hepatotoxicity was assessed by quantifying the activity of serum GPT. The measurements were performed by a spectrophotometric analysis automatic chemistry analyzer (Covas mira, Roche, Germany). The serum GPT level was measured according to the IFCC method.[42,43)]

6. Survival time of mice injected with chemo-therapeutic agents

The survival time was determined over 5 weeks after injecting the 5-FU or cisplatin. The 5-FU (50 mg/kg) and cisplatin (10 mg/kg) were injected into the peritoneal cavities of the mice 3 times at 2 day intervals after 3 weeks of *Saengshik* administration, and then the *Saengshik* was fed one additional week.

7. Statistical analysis

The data analysis was performed using SPSS version 10.0 software (SPSS, USA). All values are expressed as mean±SD, and were compared using one-way ANOVA. Values of $P < 0.05$ were considered significant. Post-hoc analysis of the differences in mean values for each experimental group were compared and analyzed using Duncan's method.

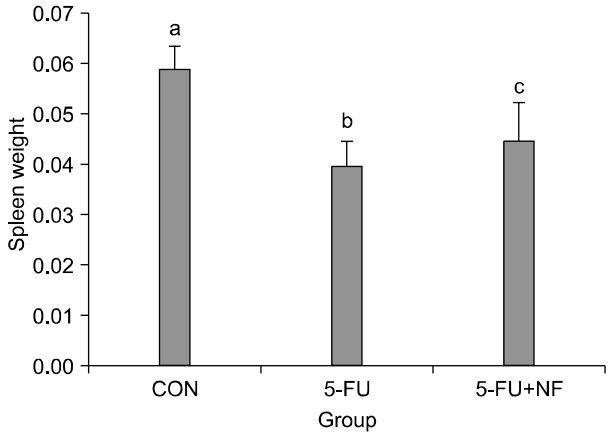
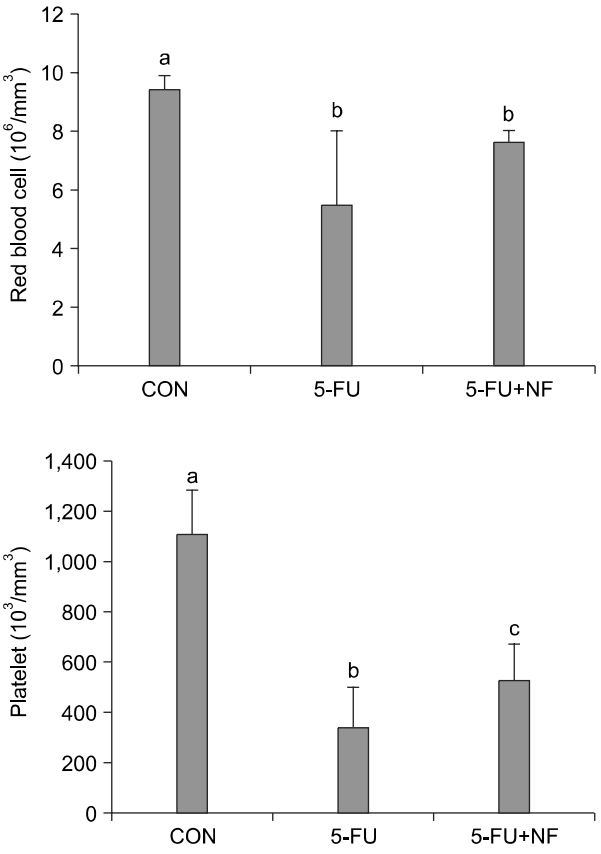


Fig. 1. Inhibitory effects of *Saengshik* administration on decreases of spleen weight in 5-FU administered C57/BL6 mice. The 5-FU and 5-FU+*Saengshik* groups were injected with 200 mg/kg of 5-FU intrapeneally after one week of diet administration, and the diet was then fed an additional week. Means with same alphabet was significantly not different ($p<0.05$). 5-FU: 5-fluorouracil, NF: *Saengshik* administration.

RESULTS AND DISCUSSION

1. Alleviative effects of *Saengshik* on the side effects of single-dose 5-FU administration

1) The inhibitory effects of *Saengshik* on decreases in spleen weight: The spleen is an organ located in the abdomen, where it functions in the destruction of old red blood cells and holds a reservoir of blood. It is regarded as one of the centers of activity for the reticuloendothelial system (part of the immune system). The size and function of the spleen is weakened during chemotherapy due to splenocyte death and spleen tissue reductions.[44,45] The spleen weight was markedly reduced (about 30%) after 5-FU injection as compared to the control group, while there was a 10% reduction after 5-FU injection with *Saengshik* administration. This indicates that *Saengshik* had effects against decreasing spleen weight, one of the side effects of chemotherapeutic agents (Fig. 1).



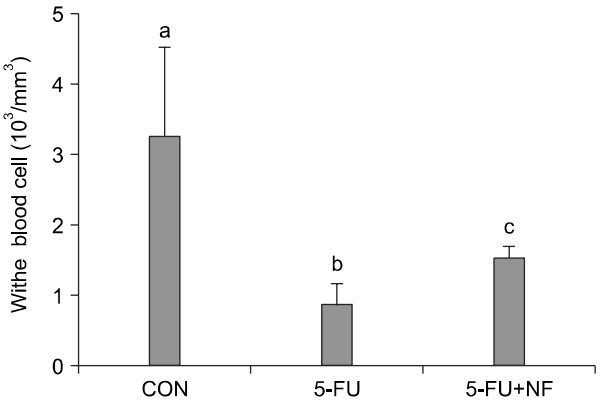


Fig. 2. Results of hematological examinations in *Saengshik* administered C57/BL6 mice. The 5-FU and 5-FU+*Saengshik* groups were injected with 200mg/kg of 5-FU intrapeneally after one week of diet administration, and the diet was then fed an additional week. Collected whole blood cells were automatically counted by an automatic blood cell counter. Means with same alphabet was significantly not different ($p<0.05$).
5-FU: 5-fluorouracil, NF: *Saengshik* administration.

2) Inhibitory effects of *Saengshik* on decreases in blood cell counts: Fig. 2 shows the results of the red blood cell (RBC), white blood cell (WBC), and platelet (PLTs) counts in the peripheral blood of the heart. While the total peripheral RBC, WBC, and PLT numbers clearly decreased in the 5-FU administered mice, the effects were inhibited after *Saengshik* administration. Decreases in RBCs (37%), WBCs (72%), and PLTs (83%) were shown after 5-FU injection. It was verified by the colony forming assay that 5-FU reduced the whole blood cell counts and damaged the hematopoietic stem/progenitor cells (data not shown). However, the RBCs were increased 34% in the 5-FU+*Saengshik* group as compared to the group treated with 5-FU only. The WBCs and PLTs were increased 12% and 57%, respectively (Fig. 2). Based on the above results, *Saengshik* administration proved to have a protective effect on hematopoietic cell damage.

3) Improvements in serum GPT levels by *Saengshik* administration: The serum level of glutamic pyruvic transaminase (GPT) is a cytosolic marker reflecting hepatocellular necrosis, as GPT enzymes are released into the blood after cell membrane damage. Chemotharapeutic agents are reported to cause severe hepatotoxicity, and damage fast- dividing normal cells. Compared with the control group, the serum GPT level was reduced in the *Saengshik* group, while the level was significantly increased in the 5-FU and cisplatin injected groups. GPT was decreased approximately 38% in the *Saengshik* group as compared to the 5-FU treatment group (Fig. 3). Therefore, *Saengshik* administration proved to have an anti-hepatotoxicity effect.

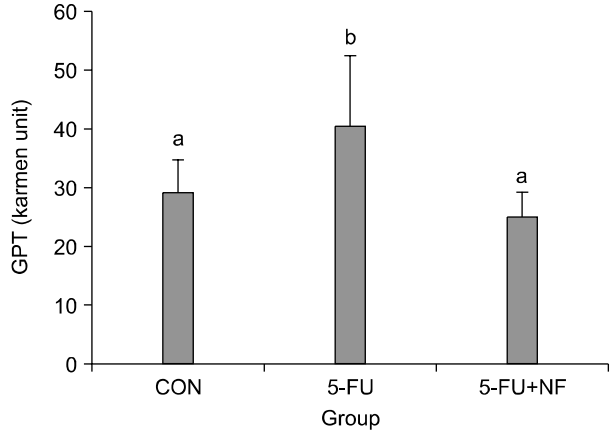


Fig. 3. Preventive effects of *Saengshik* administration on serum GPT levels in 5-FU administered C57/BL6 mice. The 5-FU and 5-FU+*Saengshik* groups were injected with 200 mg/kg of 5-FU intrapeneally after one week of diet administration, and the diet was then fed an additional week. Whole blood cells were collected from the heart of the mice and serum were separated by centrifugation. GPT levels measurements were performed by a spectrophotometric analysis automatic chemistry analyzer. Means with same alphabet was significantly not different ($p<0.05$).
5-FU: 5-fluorouracil, NF: *Saengshik* administration.

2. Alleviative effects of *Saengshik* on the side effects of multiple-dose 5-FU or cisplatin administration

1) The inhibitory effects of *Saengshik* on decreases in spleen weight: Usually chemotherapy is treated repeatedly and in combination, so we examined the multiple-dose administration of the two kinds of chemotherapeutic agents. 5-FU or cisplatin were treated 3 times at 2 day intervals. The triple administration of 5-FU or cisplatin brought 57% and 63% reductions in spleen weight, respectively, as compared to the control group (Fig. 4). The repeated treatment of 5-FU showed a 57% reduction, as compared to a 30% reduction during short-term administration. This indicates that the multiple-dose administration of the chemotherapeutic drugs brought continuous severe damage to the mice. The *Saengshik* administered group showed an inhibitory effect for spleen weight reduction. *Saengshik* administration in the 5-FU group

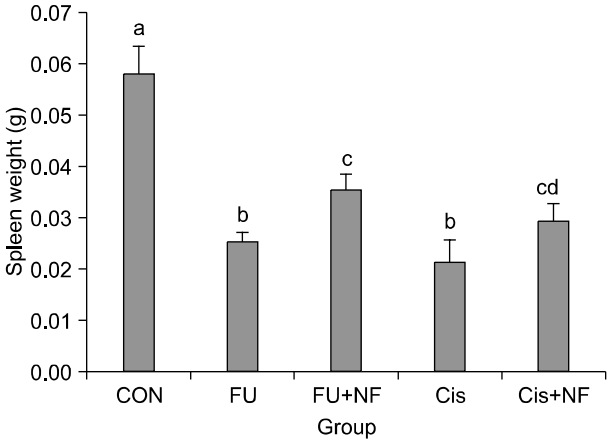


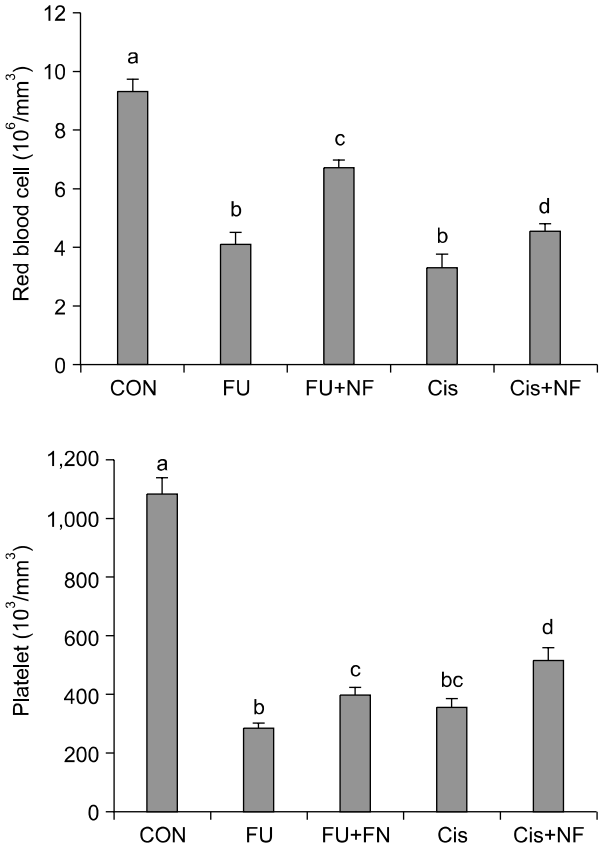
Fig. 4. Inhibitory effects of *Saengshik* administration on spleen weight in C57/BL6 mice. The *Saengshik* was administered for 3 weeks and the 5-FU (50 mg/kg) or cisplatin (10 mg/kg) was injected 3 times at 2 day intervals, and then the *Saengshik* was fed one more week. Means with same alphabet was significantly not different ($p<0.05$).
5-FU: 5-fluorouracil, Cis: cisplatin, NF: *Saengshik* administration.

resulted in a 40% increase in spleen weight, and *Saengshik* administration in the cisplatin group resulted in a 38% increase; while at 2 weeks of *Saengshik* feeding there was only a 10% increase in spleen weight in Fig. 1. This indicates that the long-term administration of *Saengshik* had a much greater effect on the side effects of chemotherapy than the short feeding.

2) Inhibitory effects of *Saengshik* on decreases in blood cell counts: We also explored the effects of Saengshik on blood cell counts. For the RBCs, the 5-FU and cisplatin groups had 57% and 53% reductions, respectively. The reduction numbers for the WBCs were 73% in the 5-FU group and 58% in the cisplatin group, and the platelet number reductions were 75% and 68%, respectively. This data also indicates that more severe damage was brought on by the multiple-dose administration of the chemotherapeutic agents. On the other hand, *Saengshik* administration prevented the reductions in blood cell counts caused by 5-FU and cisplatin. The RBC numbers were maintained 53% and 20% in the 5-FU and cisplatin groups, respectively. The WBC numbers were maintained 43% and 42%, respectively, and the platelet numbers were maintained 42% and 47%, respectively (Fig. 5). These results indicate that the long-term administration of *Saengshik* had better affects on the side-effects of the chemotherapeutic drugs than short-term administration, suggesting that continuous intake of *Saengshik* alleviated the side effects of chemotherapy.

3) Improvements in serum GPT levels by *Saengshik* administration: We investigated the effects of *Saengshik* administration against the hepatotoxicity caused by 5-FU and cisplatin. The preventive effects of the multiple administration of *Saengshik* on GPT were observed (Fig. 6).

4) Improvements in survival rate by *Saengshik* administration: Continuous chemotherapy brings numerous side-effects, as stated above, and can ultimately cause death. Recently, Ohe Y et al. reported that chemotherapy in cancer patients has the risk of treatment-related death.[46,47] We observed survival time over 5 weeks, following the injection of 5-FU 3 times intraperitoneally and the administration of *Saengshik*. The survival times of the mice were prolonged after *Saengshik* administration. The 5-FU or cisplatin only administered groups had 40% and 70% survival rates, respectively,



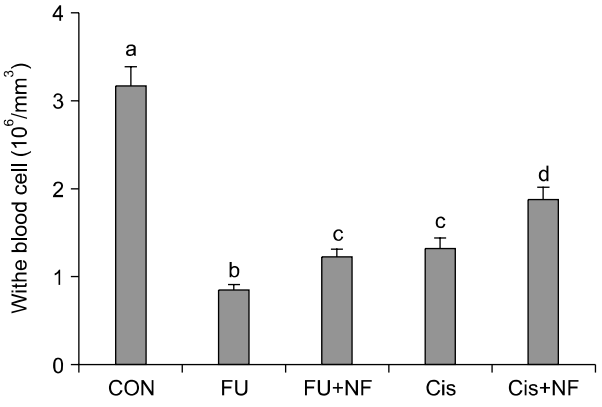


Fig. 5. Results of hematological examinations after *Saengshik* feeding in 5-FU or cis treated C57/Bl6 mice. The *Saengshik* was administered for 3 weeks and the 5-FU (50 mg/kg) or cisplatin (10 mg/kg) was injected 3 times at 2 day intervals, and then the *Saengshik* was fed one more week. Collected whole blood cells were automatically counted by an automatic blood cell counter. Means with same alphabet was significantly not different ($p<0.05$).
5-FU: 5-fluorouracil, Cis: cisplatin, NF: *Saengshik* administration.

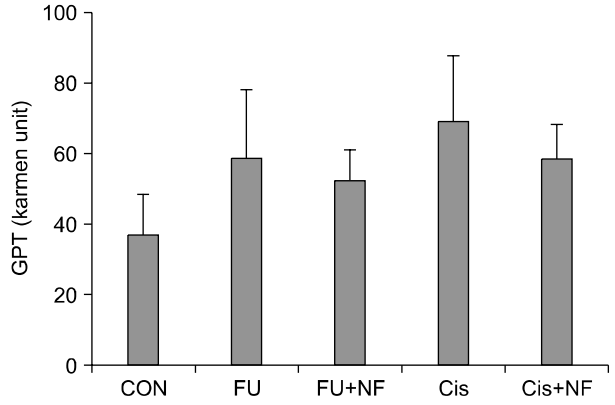


Fig. 6. Preventive effects of *Saengshik* administration on serum GPT levels in 5-FU administered C57/BL6 mice. The *Saengshik* was administered for 3 weeks and the 5-FU (50 mg/kg) or cisplatin (10 mg/kg) was injected 3 times at 2 day intervals, and then the *Saengshik* was fed one more week. Whole blood cells were collected from the heart of the mice and serum were separated by centrifugation. GPT levels measurements were performed by a spectrophotometric analysis automatic chemistry analyzer. Values shown represent the Mean±SD. 5-FU: 5-fluorouracil, Cis:cisplatin, NF: *Saengshik* administration.

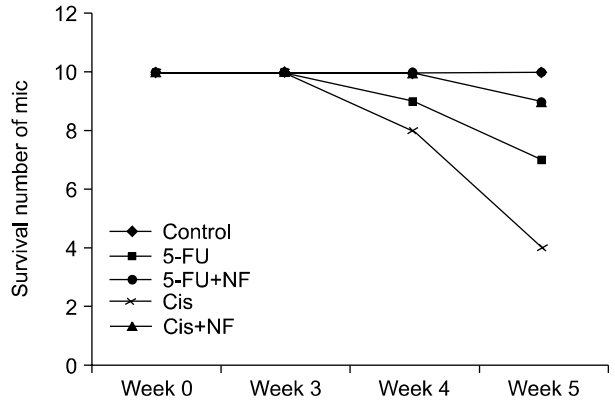


Fig. 7. Improvement of survival rate in *Saengshik* administered C57/BL6 mice. Survival time was observed over 5 weeks, following the injection of 5-FU 3 times intraperitoneally and the administration of *Saengshik*. 5-FU: 5-fluorouracil, Cis:cisplatin, NF: *Saengshik* administration.

for the survival time over 5 weeks. However, the survival rate was prolonged to 90% in both the *Saengshik* + 5-FU group and the *Saengshik* + cisplatin group (Fig. 7).

Many reports have supported that functional plant materials have interactions with chemotherapy drugs. Modified forms of vitamin A and vitamin C were reported to work synergistically with chemotherapy, and appear to increase the effectiveness of chemotherapy.[12~14] Furthermore, the combination of several vitamins protected against chemotherapy-induced heart damage without interfering with the action of the chemotherapy.[15] In studies of chemotherapy-induced mouth sores, many researchers have confirmed the potential for vitamin E to help people with chemotherapy-induced mouth sores.[48~50] Studies on glutathione have found that glutathione may decrease some of the adverse effects of chemotherapy and radiation.[41,51] And dietary glutathione intake from fruits and raw vegetables has been associated with protection against some forms of cancer.[51,52] Marco K et al. also found certain polysaccharides to be helpful for the cytotoxicity of chemotherapeutic agents.[53]

Table 3. Nutrients contents in *Saengshik*

Nutrients	Contents
Energy (kcal/100 g)	392.6
Moisture (%)	1.9
Carbohydrate (%)	80.9
Protein (%)	11.4
Fat (%)	2.6
Na (mg/100 g)	176.5
Fe (mg/100 g)	3.54
Zn (mg/100 g)	7.83
Ca (mg/100 g)	600
Vitamin A (ugRE/100 g)	368.7
Vitamin B1 (mg/100 g)	1.8
Vitamin B2 (mg/100 g)	0.4
Vitamin B6 (mg/100 g)	0.4
Vitamin C (mg/100 g)	43.5
Vitamin D3 (mg/100 g)	21.6
Vitamin E (mg/100 g)	5.1
Folic acid (mg/100 g)	1.9
Niacin (mg/100 g)	9.9

Saengshik includes a variety of grains, vegetables, fruits, mushrooms, and sea plants, and has diverse nutrients, as shown in Table 3. It is whole, and contains a variety of nutrient-dense plants with phytochemicals and complexes only found in natural foods. It is considered that the various functional plant materials in *Saengshik* may have a relief effect on the side effects of chemotherapy.

Cancer patients receiving chemotherapy undergo loss of appetite and malnutrition, and declines in body strength are a result. When blood cells are affected by anticancer drugs, patients are more likely to develop infections, may bruise or bleed easily, and may have less energy. So in cancer patients receiving chemotherapy, appetite promotion, body weight maintenance, and the prevention of immune system weakness and infection are quite important.[54]

Park SH et al. and Lee YJ et al. reported that *Saengshik* improved nutritition status.[34,35] In addition, Park JY et al. reported that *Saengshik* exhibited superior activity for improving mesenteric lymph node immune function in nutritionally unbalanced rats.[32] It is suggested that the nutrients of *Saengshik* are also helpful for alleviating the side-effects of chemotherapy. In conclusion, *Saengshik* had a relief effect on the side-effects of cancer chemotherapeutic agents, including hematotoxicity, hepatotoxicity, and death rates in mice.

CONCLUSION

The aim of this investigation was to evaluate the preventive effects of *Saengshik* on the side-effects of chemotherapeutic agents. To induce the side effects, 5-FU or cisplatin were administered, and the hematotoxicity and hepatotoxic effects were explored. The *Saengshik* administration showed a relief effect for the side effects of 5-fluorouracil (5-FU) and cisplatin in mice, by preventing decrease of spleen weight and numbers of blood cells. Also, the preventive effect administration of *Saengshik* on GPT was observed, and survival time was prolonged after 5-FU or cisplatin injection with *Saengshik* feeding. These data suggest that *Saengshik* may prove to be helpful in cancer patients receiving chemotherapy, by alleviating the side-effects of anti-cancer agents.

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