消積白朮散의 抗癌效果 및 Cisplatin副作用 減少에 미치는 影響

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요 약

消積白朮散은 《和劑局方》에 記載된 蔘苓白朮散에 淸熱解毒藥인 瓦松 金銀花 蒲公英을 加味한 處方으로, 本方인 蔘苓白朮散은 脾胃虛弱, 飮食不振, 多困少力, 中滿痺壹, 心柾氣喘, 嘔吐, 泄瀉, 傷寒咳嗽를 治療目的으로 쓰여 온 以來 임상에서는 大便不實, 久泄, 癰疽潰後 不思食者를 治療하는데 多用되어왔다.

腫瘍(Neoplasia)은 새로운 成長(New+ Glowth) 이라는 뜻으로 細胞學的으로 非正常細胞의 過多增殖으로 인해 實質臟器, 有腔腸器 및 骨格, 皮腐組織에 非正常組織을 形成하는 疾患이다.

現代的 腫瘍과 類似한 韓醫學的인 病症은 《素問》에서는 "厥疝, 伏梁, 息積"으로 《靈樞》에서는 "腸覃, 石瘕"로 表示된 以後로 巢元方은 癥瘕, 食噎, 石癰, 緩疽, 石疽 등으로 表現하였다.

原因에 對해서는 《內經》에서는 虛와 寒氣, 寒·熱로 보았고, 그 外의 學者들은 內虛와 氣血不順, 火, 寒, 氣鬱, 陰陽不和등으로 보았다.

治療는 《內經·刺法論》에서 "正氣在內 邪不可干"이라 하여 生命活動의 原動力인 正氣의 役割을 强調하였고, 《六元正氣大論》에서는 "大積大聚 不可犯也 衰其太半而止"라 하여 攻伐藥을 過用하여 正氣를 損傷시켜서는 안된다고 하는 등 扶正爲主, 祛邪爲主 혹은 扶正祛邪 兼用의 方法이 混用되고 있다.

現代 西洋醫學의 抗癌劑는 治療效果는 優秀하지만 惡心, 嘔吐를 비롯하여 骨髓抑制效果와 肝, 心, 腎, 肺의 損傷을 招來하는 等의 副作用을 나타내며, 頻繁한 化學療法劑의 投與로 因한 癌細胞의 藥劑抵抗性 出現등이 抗癌劑의 問題點으로 提示되고 있다.

이에 著者는 脾胃機能을 强化시켜 正氣形成에 깊이 關與하는 蔘苓白朮散에 淸熱解毒, 消腫散結之劑인 金銀花, 蒲公英, 瓦松을 加味하여 癌發生 白鼠에 投藥한 後 sarcoma 180癌細胞에 對한 生命延長效果와 抗癌劑의 一種인 cis-platin을 利用하여 洋方抗癌劑의 副作用에 對한 本 方의 效果를 實驗하여 觀察하였던 바 다음과 같은 結論을 얻었다.

1. 消積白朮散은 sarcoma 180 癌細胞 移植腫瘍에 對해 生命延長效果가 認定되었다.
2. 消積白朮散은 治癌劑인 cis-platin 致死毒性에 對해 生存延長效果가 認定되었다.
3. 消積白朮散은 cis-platin 腎毒性 생쥐 및 흰쥐에 있어서 有意性 있는 體重減少抑制效果 및 serum BUN 上昇抑制效果가 認定되었다.

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4. 消積白朮散은 cis-platin 腎毒性 흰쥐에 對해 有意性 있는 serum creatinine 上昇抑制效果가 나타났으며, cis-platin의 血液學的 副作用인 RBC,WBC 減少에 對해 減少抑制效果가 認定되었다.

5. 消積白朮散은 cis-platin 腎毒性 흰쥐에 對해 尿量減少抑制 效果 및 urea nitrogen과 creatinine 排泄減少抑制效果가 觀察되었다.

以上의 結果로 부터 消積白朮散은 惡性腫瘍治療 및 抗癌劑의 副作用을 輕減시키는데 應用할 수 있을 것으로 思料된다.

I. Introduction

While an average length of human life has been extended gradually, in proprtion to this, the outbreaking frequency of all kinds of tumors, has increased rapidly these 50 years and the death-rate from cancer is getting higher and higher.

Accordingly, regardless of Orient and Occident, research for cancer is vigorusly going on, also development for new anti-cancer medicines is in progress.

However, it is a critical subject to diminish the side-effects bringing about not only sickness and vomiting but also bone marrow restraint diffect and damage to liver, heart, kidney, lung.[1)]

Since cancer was first recorded "Accumulation" at 《Nae Kyung.內經》[2)] in Oriental edicine, it has been called variously such as Jingga(癥瘕), Banwee(反胃), Eolgyuk(噎嘔), but there are many medical treatments, in short, two methods exist: one is abandoning -wrong method including ridding- fever, counteracting-poison, ctivating-blood, ri dding-bruise, smoothening and harden ing phlegm, the other is helping-good method including adding-energy, compen sating-blood, amping-negative, warming-positive, strengthening-marrow, smoothe ning stomach etc.[3-7)]

SBS Ex. is a treatment adding Orostachys Herba, Lonicerae Flos, Taraxaci Herba to Samryung Backchul san(蔘苓白朮散) and the latter improves the symptoms of appetite loss, vomiting, loose bowels, consequenthy, strengthens the spleen and smooths the stomach, so helps correct them, the former deprives the fever and counteracts poison, in addition has an anticancer effect experimentally.[8-12)]

As I prove the effect of Amti-Cancer drygs by experiment and think there would be a better increasing effect for medical treatment through the mutual cooperation between Orient and Occident, so I report the remarkable results acquired by observing the improvement effects of anti-cancer activity in virtue of the side-effcts reduction in Occidental cancer drugs by means of mixing the cancer drug cis-platin with SBS Ex. applied as a Chinese medicine for anti-cancer.

II. Experiment

1. Materials and Animals

1) Materials

The materials used in this test are carefully selected ones from Oriental Medical Hospital of Taejon University, presciptions are as follows:

Ginseng Radix alba --- 8g
Glycyrrhizae Radix --- 6g
Atradylodes Rhizoma alba --- 6g
Hoelen --- 6g
Coicis Semen --- 6g
Dolichoris Semen --- 4g
Nelumbinis Semen --- 4g
Amomi Semen --- 4g
Platycodi Radix --- 4g
Orostrachys Herba --- 15g
Lonicerae Flos --- 8g
Taraxaci Herba --- 8g
Dioscoreae Rhizoma --- 8g
Total 87g

2) Preparation of Sample the adhesive material 402.8g yield by pressing down through rotary evaporator after dividing the above mentioned quantity of prescription 20 packs, boiling, in water 3 times per 3 hours, was used in dilution necessary for this test.

3) Animals

Animals were 5-week old mice(male)in cental animal ICR line, 160-180 gram rats in Sprague Dawley Solid feed by Samyang Oils and Fats Feed Co. was used, water was sufficiently supplied affer 2 weeks adaption to the testing surrounding.

Testing was performed at 24±2 ℃ as long as no other indications were specified.

2. Method

1) Anti-Tumor Action[13-15)]

Transplanted Sarcoma 180 cancer cell 1 × 106 cell/mouse to 5 week-old mice in ICR line, continously injecting the after 24 hours, getting the average survival days and increase in MST over control by daily observation for survival on the contrary, injected saline to the comparing group, sample 0.5g/kg, 1.5g/kg to oral administration respective ly.

median survival time

ILS (Increase in MST over control)

$$= (T/C-1) \times 100$$

T : MST for Testing Group

C : MST for control group

2) Side-Effects of Anti-Cancer drugs cis-platin[16-20)]

①Action of cis-platin fatal poisoning observed the survival increase existence of SBS extract by subcutaneous injecting the equivalent quantity, cis-platin 45 ㎛/kg (13.5mg/kg). Injectded the SBS Ex. extract to oral by 0.5g/kg and 1.5g/kg one time per day for 7days starting the second day before injection to the fourth day after injection, observed the survival existence daily till the thirteenth day after SBS Ex. extract injection. Injected saline to the control group instead of SBS Ex. extract.

②Reducting Action to cis-platin side-effects

a)Action of Weight-Changes and kidney poisoning on mice

While subcutaneous injected cis-platin 35/㎛/kg, injecting SBS extract 0.5g/kg

and 1.5g/kg to oral one time per day for 10 days between 5 days before and 4 days after cis-platin injection, injected the control group saline, measuring the weight-changes daily and BUN from blood plasma pulled out at fifth day after cis-platin plasma pulled out at fifth day after cis-platin injection by far-east UN-V reagent(kit reagent).

b)Reducting Acton to Side-Effects in Rats

Subcutaneous injected cis-platin 35 ㎛ /kg, injected Sample one time per day for 10 days between 5 days before cis-platin injection 4 days after cis-platin injection, injected a physiological solution of salt. Measuring weight-changes daily, red blood-cell and white blood-cell pulled out at heart on the fifth day after cis-platin injection, BUN, creatinine and GOT, GPT in blood plasma by centrifugal separation for 15 minutes at 3000 rpm. Also measured urine amount, urea nitrogen and creatinine in urine by collecting urea nitrogen and BUN by far-east UN-V reagent, creatintine by creatinine SET(Yatron), GOT,GPT by measuring reagent for serum Transaminase manufactured in Asan Pharmacetics Co. In measuring WBC, read the blood graduation exactly to 0.5 scale by WBC pipette, counted RBC by microscopic method after diluting liquid(glacial acetic acid 3ml, 1% aqueous gentian violet 1ml, dis-tilled water) and filling in counting chamber.

Ⅲ. Results

1. Anti-tumor Effect

After observing the survival increase effect of SBS extract on Sarcoma 180 cancer cell, found Sample 0.5g/kg and 1.5g/kg injecting group transplanted sarcoma 180 cell showed 22 days and 27 days, of average survival days respectively, while control group injected only saline showed 18 days of average survival days, so the former indicated 202.2% and 50.0% of survival increase rate in comparison to the control group.

2. Alleviative Effect on cis-platin Side-Effects

1)Effect on cis-platin fatal poisoning

As shown in Table II, effect of Sample on fatal cis-platin showed control group died 70% on the sixth day after injecting cis-platin, SBS extract 0.5g/kg and 1.5g/kg injected group 30%, 0% death-rate, at the last observing day, the thirteenth day of injection, contol group survived 20%, SES extract 1.5g/kg injected group survived 90%.

2)Alleviative Effect on cis-platin Side-Effects

①Effect on Mouse Weight-Changes and Kidney-Poisoing

Measuring numbers of weight-Changes and serum BUN on inducing kidney poisoning mouse after subcutaneous injecting cis-platin 35㎛/kg are shown in Fig. 1 and Fig. 2 respectively. Namely, found they showed persistent weight-loss by subcutaneous injecting cis-platin 35㎛/kg, besides control effect for quantity dependent weight-loss by infecting SBS extract. For serum BUN

values, indicated meaningful (P <0.001) increase effect by injecting cis-platin, meaningful (P <0.05) serum BUN increase control effect in comparison to control group (cis-platin alone injecting group) by injecting SBS extract.

②Reduction Effect on kidney-poisoning and hematological side-Effects at white Mouse.

a)Weight-Changes

Showed persist weight-loss similar to the case of mouse by subcutaneous injecting cis-platin 35 ㎛/kg at rats, could observe the indication of control effect on weight loss to quantity dependent cis-plation of SBS extract.

b)Serum BUN

While normal group showed serum BUN values about 16mg/dl, could come to know meaningful (P <0.01, P <0.001) increase operation indication each 50m/dl and 150mg/dl at the third and fifth day after injection at SBS extract 1.5g/kg injecting group (Fig.4)

c) GOT and GPT Activity

As measurement for serum GOT and GPT activity shown in Table III, it concluded that cis-platin 35 ㎛/kg subcutaneous injection made little effect on serum GOT and GRT activity, SBS extract injected group didn't show any different activity.

d) Effect on Serum Creatinine levels

In Serum Creatinine levels, normal group showed 1.45mg/ dl, for cis-platin 35 ㎛/kg sububcutaneous injected group found meaningful(P <0.01) increase by injecting cis-platin because of showing 2.25mg/dl, 5.5mg/dl at the third day and fifth day, indicated meaningful (P < 0.05) serum 1.5g/kg injection for 10 days. (Fig.5)

e) Effect on RBC and WBC

As shown in Table Ⅳ, found numbers of RBC and WBC reduced meaningfully (P < 0.01) by injecing cis-platin injecting SBS extract, accepted meaningful WBC reduction-control 0 effect in SBS extract 1.5g/kg injected group.

f) Effect on urine volume

As shown the roughly measured urine quantity for 24 hours in Fig.6, found persistent remarkable urine reduction by cis-platin injection, observed quantity dependent urine reduction control operation of SBS extract.

h) Effect on Creatinine levels in Urine

As measuring creatinine excreted in urine for 24 hours, only cretinine injected control group showed remarkable reduction of creatinine excretion quantity in comparsion to normal group, accepted meaningfulness by SBS extract injection, but appeared control operation to creatinine excretion reduion induced cis-platin. (Fig.8)

Ⅳ. Discussion

On operation to sarcoma 180 cancer cell used widely as one method of experimental anti-cancer drugs as well as reduction operation to side effects of cis-platin used as treatment-cancer drugs, follows as considerations testing to extracts of SBS Ex. aquired by above mentioned at Chapter Experiment.

In cancer cell of in vivo examination on anti-cancer drugs, there exist Sarcoma 180A, P-388 Leukemia, L1210 Leukemia, C1498 leukemia, Ehrlich Carcinoma, Mammary Carcinoma, B-16 Melanoma, Lewis lung Carcinoma, Colon-38 Adenocarcinoma. The most used transplant-type tumor at plant extracts and synthetics inspection in 1950's was Sarcoma 180(SA), Adeno carcinoma 755(CA), Leukemia L1210 (LE).[21]

In middle 1920's, has been reported walker Sarcoma 256(WA) and Lympha tic Leukemia P388 System was used commonlky,and the first examination policy was first examined to P388 Leukemia, then to another tumor in turn.

In order to watch survival increase effect on sarcoma 180 cancer used frequently as screen method of anti-cancer drugs, 10 days, consecutive injection of testing liquids resulted in 50% survival increase, accordingly accepted survival increase effect on sarcoma 180 cancer.

Cis-platin used widely as treating-cancer drugs is a adhesive material, which has a system central platium atom constituting cis-position including 2 chlonines and 2 ammonia atomic units.

Cis-platin was reported it had mutual relation with cis-platin experimentally as its combination with DNA and with it prevents division of cancer cells, has an influence on Metastatic Testicular tumor, Metastatic Ovearian Tumor, Boadder Carcinoma, Cancer of Head Neck, also that cis-platin prevents DNA composition in animal tumor test has been reported DNA and cis-platin composes cross-links formation.[21-22]

Side-effects of cis-platin are, the most poisonous place is kidney, in addition because of side effect of hematolgic, Gastrointestinal and ototoxicity an evil intention, vomiting, loose bowels, stomachache, reduction disease of haemoglobin, red blood cell, white blood cell owing to Myelosupression.

So, thought it the most important problem that we should diminish side effects in cis-platin injection as treating cancer drugs, taking in to consideration prescrcptive drugs of SBS extract are mainly ridding-fever counter, acting-poison materials after observed survival increase, existence of SBS extrat to cis-platin to watch reduction effect on cis-platin side effects, the survival numbers of the last observing day, the 13th day, increased by 70% by consecutively injecting SBS extract for 7 days in comparison to control group only cis-platin 45 ㎛/kg subcutaneous depend ent survival increase effect of SBS extract.

As cis-platin brings about remarkable kidney-poisoning, in order to examine reduction brings about remarkable kidney-posoning, the most favorable kidney-posoning happened by cis-platin 35㎛/kg subcutaneous injection investi gated effect of SBS extract using mouse, and found persistent weight loss through cis-platin injection as well as weight loss control effect through injection of SBS extract in weight

changes.

During testing period, observed the symptom of loose bowels, tendency of not gaining food well, which I regarded was from side effects of digestive organs by cis-platin injection in measuring serum BUN levels regarded as screen test, in SBS extract injection group accepted meaningful increase control effect for BUN.

In order to observe not only kidney poisoning of cis-platin but also reduction effect of SBS extract to hematological side effects, measured weight changes, serum GOT, GPT, RBC, WBC by way of rats to be pulled out necessary blood for test, also largely measured urine volume, urea nitrogen in urine and creatinine.

Observed weight changes and effect of SBS extract to serum BUN lebel were similar to the case using mouse.

Urea is a final production in protein renewal, which is formed in liver, recrected as urine, by measuring serum GOT, GPT, as it did not influence any toxicant effect on liver, think BUN increase in blood contribuences to recretion control as urine.

BUN as a indication of kidney function inspection is changed by various factors, so primarily used in measuring kidney function.

By observing hematologic effect on serum creatinine lebels, in comparing group, could find the kidney function reduced through meaningful rise of serum creatinine, in injection group of SBS extract accepted increase control operation of serum creatinine. As cis-platin brings about reduction symptom of white and red blood cell due to bone marrow control, in observing injection of SBS extract on RBC, WBC, control group showed meaningful reduction operation of RBC, WBC, however injection group of SBS extrat showed reduction control effect on RBC, WBC.

Effect of SBS extrat on urine volume for 24 hours indicated reduction control effect on urine reduction by cis-platin, in measuring urea nitrogen and creatinine recreted to urine, showed remarkable recretion quantity by injection of SBS extrat.

As mentioned above, SBS extrat showed survival increase effect on Sarcoma 180 cancer cell, reduction effect on fatal toxication and side effect of treating cancer drugs, cis-platin, so think development for cancer treatment would come true, in future expect to research constantly on effective evaluation of chinese medicine toward reduction of side effect on western medicine or immunity reinforcement.

V. Conclsion

With a view to observing anti-cancer effect of SBS extract and reduction effect of side effects in anti-cancer drugs of western medicine, as investigated survival increase effect on sarcoma 180 cancer cell of mice and rats, and effect on injection of anti-cancer drug cis-platin, could get following results.

1. SBS extrat was admitted survival

Table I. Effect of Sojeokbaekchool-san on lifespan of mice implanted intraperitoneally with Sarcoma 180

Groups	Dose (g/kg,p.o)	No. of animal	MST (%)	ILS (%)
Control	-	10	18	-
Sample	0.5	10	22	22.2
Sample	1.5	10	27	50.0

Table II. Effect of Sojeokbaekchool-san on Lethal Toxicity of cis-platin in mice

Groups	Dose (g/kg,p.o)	Number of survivors Days after injection of cis-platin 0	2	4	6	8	10	Survival rate (%)
Control	-	10	10	5	3	2	2	20.0
Sample	0.5	10	10	7	7	5	5	50.0
Sample	1.5	10	10	10	10	9	9	90.0

On day 0, cis-platin(45μM/kg,s.c) was injected to mice

Sample was administered to mice once a day for 7 days from day -2 to day 4.

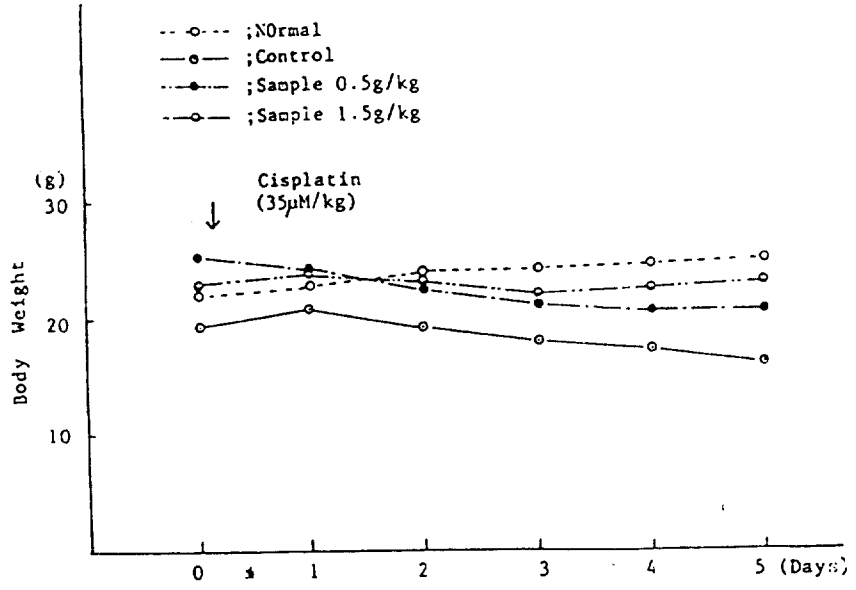

Fig. 1. Effect of Sojeokbaekchool-San on the body weight in mice

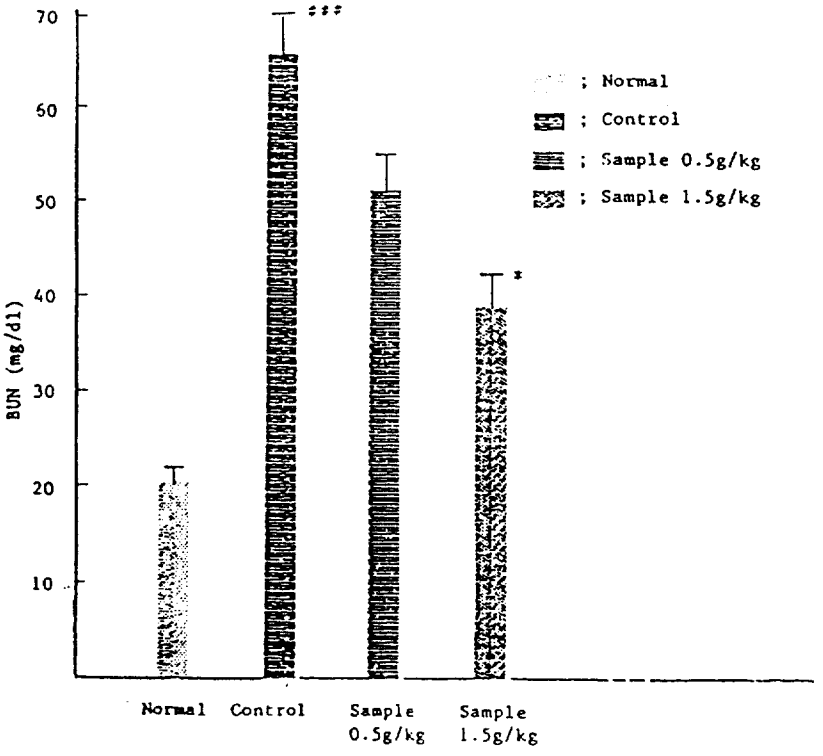

Fig. 2. BUN values of mice 5 days after injection of cisplatin
Cisplatin was injected to control and sample group (35μM/kg)
Sample were administered p.o to mice from day -5 to day 4.
: Statistical significance compared with normal group ($p < 0.001$)
*: Statistical significance compared with control group ($p < 0.05$)

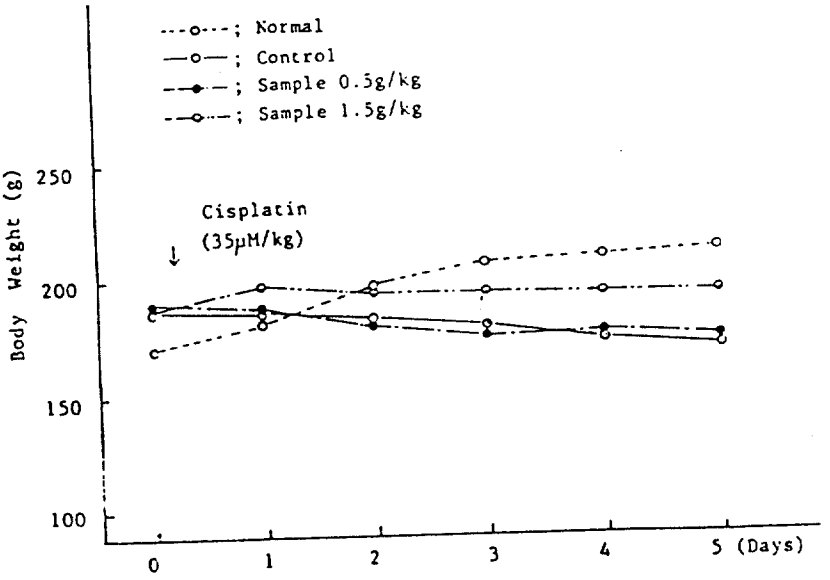

Fig. 3. Effect of Sojeokbaekchool-San on the body weight in rats
Cisplatin was injected to control and sample group
Sample were administered p.o to rats from day -5 to day 4.

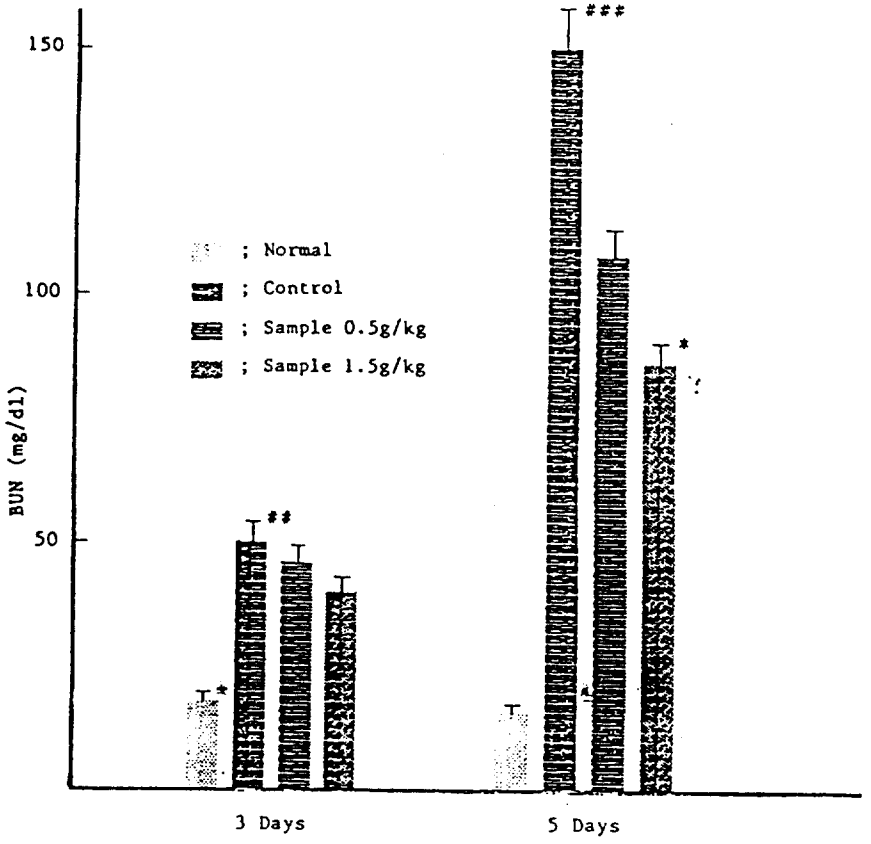

Fig. 4. BUN values of rat serume after injection of cisplatin
Cisplatin(35μM/kg,s.c) was injected to control and sample group
Sample were administered to rats once,a day for 10 days from
day -5 to day 4.

#: Statistical significance compared with normal group
(##;p< 0.01 and ###;p< 0.001)

*: Statistical significance compared with control group (p< 0.05)

Table III. GOT and GPT activities of rat serum 5 days after injected of cis-plutin in rats

Groups	Dose (g/kg,p.o)	No. of animal	GOT and GPT activities(Karmen Unit) GOT	GPT
				a)
Normal	-	8	32.4±2.42	29.0±2.92
Control	-	8	35.1±2.61	37.2±3.14
Sample	0.5	8	32.3±3.23	33.0±3.42
Sample	1.5	8	36.1±2.75	34.4±2.25

a): Mean ± Standard error

Cis-platin(35uM/kg,s.c) was injected to control and sample group

Sample were administered p.o to rat once a day for 10 days from day -5 to day 4.

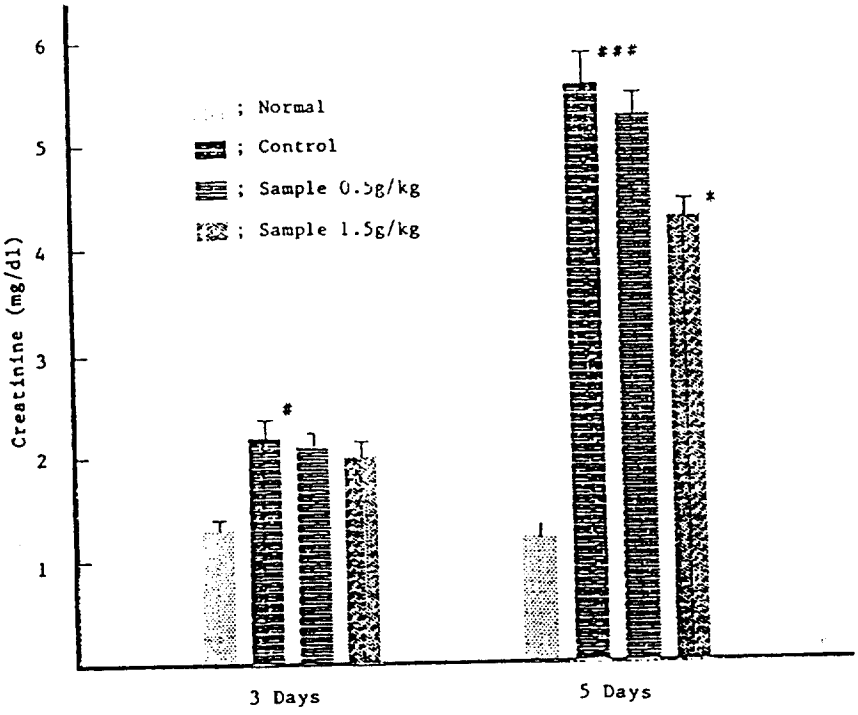

Fig. 5. Creatinine values of rat serum after injection of cisplatin
Cisplatin(35μM/kg,s.c) was injected to control and sample group
Sample were administered p.o to rats once a day for 10 days
from day -5 to day 4.
#: Statistical significance compared with normal group
(#;p< 0.05 and ###;p< 0.001)
*: Statistical significance compared with control group (p< 0.05)

Table IV. Effect of Sojeokbaekchool-san on the values of RBC and WBC 5 days after injection of cis-platin in rats

Groups	Dose (g/kg,p.o)	No. of animal	RBC(x20,000cells/㎣)	WBC(cells/㎣)
Normal	-	8	368.0±20.2	14800±1150 a)
Control	-	8	291.0±9.64 ##	7805±1220 ##
Sample	0.5	8	285.0±19.5	7550±1120
Sample	1.5	8	340.8±15.0	11375±1050 *

a): Mean ± Standard error

Sample were administered p.o to rat once a day for 10 days from day -5 to day 4

##:Statistical significance compared with normal group($p < 0.01$)

*: Statistical significance compared with control group($p < 0.05$)

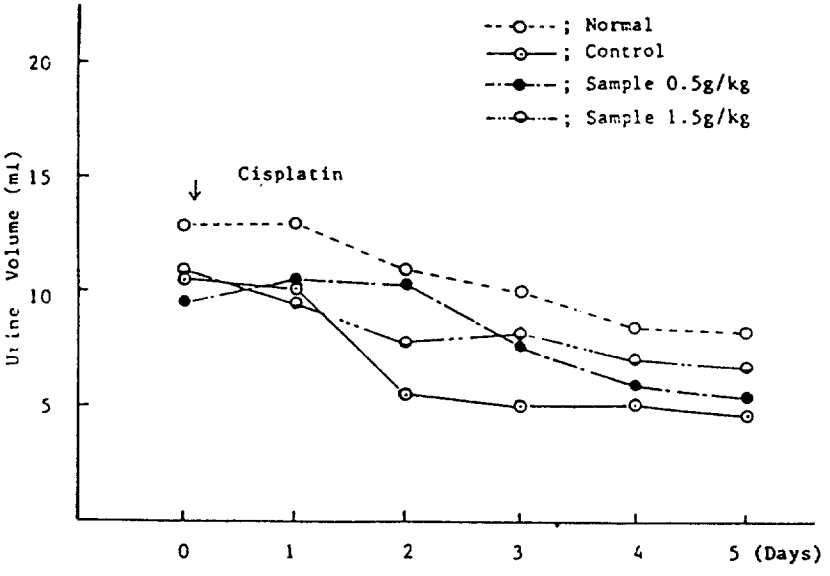

Fig. 6. Effect of Sojeokbaekchool-San on the urine changes for 24 hrs in rats

Cisplatin(35μM/kg,s.c) was injected to control and sample group

Sample were administered p.o to rats from day -5 to day 4.

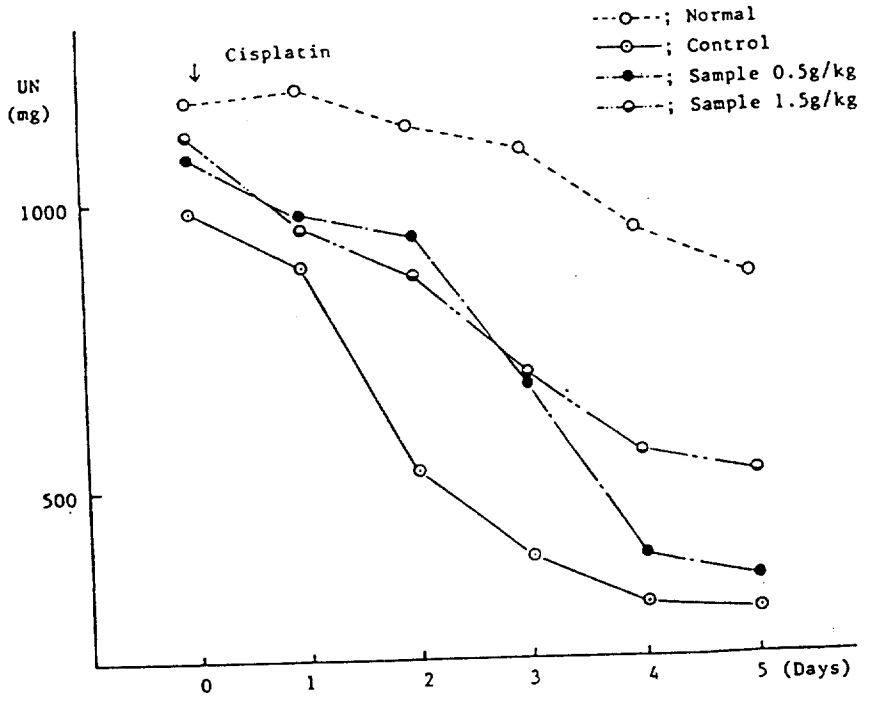

Fig. 7..Effect of Sojeokbaekchool-San on the excretion of urea nitrogen changes caused by cisplatin for 24 hours in rats
Cisplatin(35μM/kg,s.c) was injected to control and sample group
Sample were administered to rats once a day for 10 days

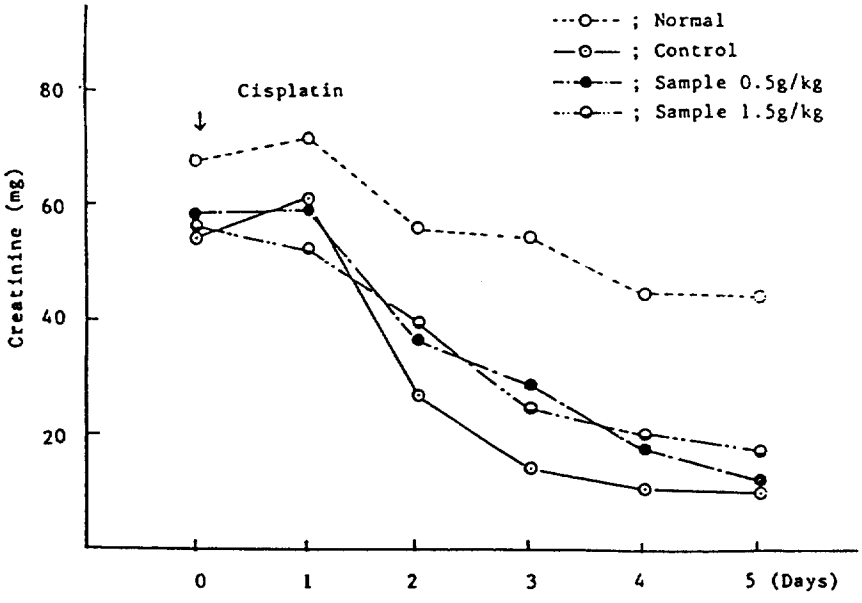

Fig. 8. Effect of Sojeokbaekchool-San on the excretion of creatinine changes caused by cisplatin for 24 hours in rats
Cisplatin(35μM/kg,s.c) was injected to control and sample group
Sample were administered p.c to rats once a day for 10 days from day -5 to day 4.

increase effect on transplanted tumor of sarcoma 180 cancer cell.

2. SBS extrat was admitted survival increase effect of fatal intoxication of cis-platin as anti-cancer drug.

3. SBS extrat was admitted reduction control effect on kidney-poisoning and weight of mouse, rat, increase control effect on serum BUN.

4. SBS extrat showed increase control effect on serum ereatinine to rat with cis-platin kidney poisoning, admitted reduction control effect on RBC, WBC reduction as hematological side effect of cis-platin.

5. SBS extrat was ovserved urine reduction control effect on rat with cis-platin kidney poisoning, recretion reduction cortrol effer of urea nitrogen and creatinine.

From above described results, think we can apply SBS exrtat to treat malignant tumor and reduce side effects of anti-cancer drugs.

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