CHAPTER 26

A NEW BIOLOGICAL RESPONSE MODIFIER SUBSTANCE - PSP

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1. INTRODUCTION

Yun Zhi is a kind of Zhi. It is part of Chinese traditional medicine and has the function of promoting one's positive factors, strengthening physique, and increasing energy and spirit (Li, 1991).

One of the main characteristics of Chinese medicines is to promote one's positive factors and to increase or adjust the body's immunological functions to prevent diseases. It is also the direction of research for the preparation and production of new anti-tumor drugs. Recently, the application of Biological Response Modifiers (BRM) in the cure of cancers has become the fourth kind of classical treatment after surgery, chemo- and radio-therapy. Frequently-used BRM substances, such as interferon, interleukin-2,PSK (krestin), lentinan, TNF, etc. are substances for regulating positive factors and removing negative factors (Joji, 1985; Chen, 1989).

From 1983 to 1992, we isolated various strains of *Coriolus versicolor* (L.ex Fr.) Qu'el from many areas in China. Strain Cov-1 was selected for further study and a polysaccharopeptide (PSP) extracted from the mycelia by means of submerged fermentation. This substance has the properties of promoting the positive factors and removing the negative factors of the human body. PSP has been investigated by means of chromatography, mass and nuclear magnetic resonance spectra: it is made up of 90% polysaccharide and 10% peptide and has a molecular weight of about 100kd. The amino acids in the peptide are mostly asparagine and glutamic acid. The main ingredient of polysaccharide is glucose and the main chain is connected by $\alpha 1 \rightarrow 4$ and $\beta 1 \rightarrow 3$ glycosidic linkages. Small amounts of galactose, mannose, xylose, arabinose and rhamnose are also present. The chemical ingredients of PSP are similar to those of Japanese PSK, but the former does not contain fucose and the latter is lacking arabinose and rhamnose (Masayoshi *et al.*, 1982; Yang & Jong, 1989).

From research into the pharmacological and clinical functions of PSP, the substrate clearly functions by promoting the positive factors and removing the negative factors of the human body and is a new kind of BRM drug. Its biological regulating functions are reported here.

2. PHARMACOLOGICAL EFFECTS OF PSP

In order to examine the mechanism(s) underlying the promotion of the positive factors and the strengthening of the physique of the organism, we examined several immunological indices in normal mice, tumor-bearing mice and mice undergoing chemotherapy.

2.1. The effects of PSP on the immunological system of normal organisms

2.1.1. The effect of PSP on the phagocytic functions of normal mice. A sample of 100 normal mice (ICR), 1/2 male and 1/2 female, was divided into 10 groups. Half were given PSP by oral administration and half by abdominal injection. There were 3 groups based on high, medium and low PSP dosages. Oral doses (0.5-1.5g/kg) were administered daily for a total of 9 days; intraperitoneal injections (100, 200, 400 mg/kg) were given daily for 4 days. After the last dose, 50% Indian ink was injected into the tail veins of the mice (5ml/kg). After 20 minutes, a 20μl blood sample was taken from behind the eye-socket and added instantly to 2 ml 0.1M Na_2CO_3 solution. The absorbance at 650nm was measured and the carbon clearance rate (K value) calculated. The results showed that the carbon clearance rate of the PSP group was similar to that of the group treated with acanthopanax (Table 1). Thus, whether administered orally or by abdominal injection, PSP clearly increases the carbon clearance rate in mice, suggesting that PSP can appreciably increase the phagocytic function of normal mice (Table 1).

2.1.2. The effects of PSP on the increase of T-lymphocytes. Cell culture solution containing 25, 50, 100, 200, 400 and 800 ug/ml PSP was used to cultivate spleen T-lymphocytes in 5% CO_2 at 37°C. After 66 hr, 0.25 μci of ^{3}H-thymidine (^{3}H-TdR) was added and, after a further 6 hr, the cells were collected and the amount of radioactivity (dpm) determined. Concentrations of PSP in excess of 100ug/ml produced a clear increase in T-lymphocytes, especially in the presence of Con A. The increase in T-lymphocytes was 1.5 to 4.0 times compared to the control group (Table 2).

TABLE 1. The effects of PSP on the carbon clearance rate of normal mice.

Group	Route	Dosage	Number of animals	K value($\overline{X}$±SD)x10^3
Physiological saline	po	0.1ml/10g	10	6.6±2.8
PSP	po	0.5g/kg	10	10.1±3.5*
PSP	po	1.0g/kg	10	11.9±3.5**
PSP	po	2.0g/kg	10	15.0±5.5**
Acanthopanax	po	300mg/kg	10	11.4±3.9**
Physiological saline	ip	0.1ml/10g	10	3.6±2.0
PSP	ip	100mg/kg	10	5.6±2.0
PSP	ip	200mg/kg	10	6.5±2.3#
PSP	ip	400mg/kg	10	6.2±1.3##
Acanthopanax	ip	300mg/kg	10	6.2±2.9#

Compared with the physiological saline group: * P<0.05, ** P<0.01, # P<0.05, ## P<0.01.

TABLE 2. The effects of PSP on the increase of T-lymphocytes.

PSPconcentration μg/ml	^{3}H-Thymidine infiltration capacity(dpm)	
	without Con A	with Con A
0	1174±227	2000±460
25	1079±230	1608±288
50	1521±169	2250±493
100	2191±154**	3435±309*
200	2082±432*	5115±1313*
400	2215±469*	8956±1631**
800	3137±694**	9204±1750**

Compared with the contrast group: *P<0.05; **P<0.01

2.1.3. The effect of PSP on the production of interferon by human blood cells. Human white blood cells (1x10^7) were cultivated at 37°C for 24 hr in solutions containing different concentrations of PSP. The cultivation was then continued for one hour after the addition of α-interferon or γ-interferon at low concentrations (200IU/ml). Next, α-interferon and γ-interferon were induced with 64-128 HAV/ml of Newcastle disease virus (NDV-F line) or 100μg/ml PHA, respectively, for 20 or 40 hours at 37°C.

The value of the effect on interferon was determined using the method involving inhibition of pathological changes in the cells, by determining the cells to be human amnionic WISH cells. Vesicular stomatitis virus (VSV) was then used as the challenge virus and the data corrected for values obtained with a standard interferon product and converted into international units. From Table 3, it is clear that PSP induces interferon in human WBC's: γ-interferon levels in the PSP group were twice those of the control group while α-interferon levels were 2-4 times higher.

TABLE 3. The effect of different concentrations of PSP on interferon induction.

Number of cases		Physiological saline contrast group	Effect value of interferon (1x10^3 IU/ml) Different concentrations of PSP for the trial group (μg/ml)			
			1	10	100	1000
α-interferon	1	4	4	8	8	16
	2	4	4	8	8	16
	3	4	4	16	16	16
	4	4	4	8	8	16
γ-interferon	1	2	2	2	4	4
	2	2	2	2	4	4
	3	2	2	2	4	4
	4	2	2	2	4	4

2.1.4. The effect of PSP on the secretion of interleukin-2 in mice. $C_{57}BL/6$ mice were administered orally with 1500mg/kg of PSP for 5 days. After dislocating their vertebra cervicalis, the mice were allowed to die and their spleens removed and ground to give a cell suspension. Tris-NH_4Cl (0.17ml) was used to lyse the red blood cells, the spleen cells were washed with RPMI-1640 nutrient solution and the cell concentration adjusted to 1 x 10^7 cells/ml. Cell survival rate was 90%.

One ml of spleen cells suspended in RPMI nutrient solution containing Con A was added to each well of a 24-well culture plate. The plate was then incubated at 37°C for 24 hr in 5% CO_2. The contents of each well were then centrifuged at 2000 rpm for 20 minutes and the IL-2 content of the supernatant determined as follows:

Nutrient solution with 15% rat factor was used to cultivate IL-2-dependent cells (CTIL-2). The cells were washed twice with RPMI-1640 nutrient solution and then suspended in 10% FCS nutrient solution to a density of 1 x 10^5 cells/ml. A 100µl aliquot of cell suspension was added to each well of a 96-well culture plate and 1:6, 1:18, 1:54 and 1:162 dilutions of the solutions from the earlier spleen cell cultivations added. The culture plate was incubated for 32 hr at 37°C under 5% CO_2. ^{3}H-Thymidine (0.5 µci) was added to each well and the cultivation continued for a further 6-8 hr after which the cells were collected using a multi-headed cell collector. After drying, the ^{3}H-thymidine infiltration capacity (dpm) was determined using a liquid scintillation counter.

The results showed that the dpm values of all four dilutions of the PSP group were clearly higher than the physiological saline control group (Table 4). Thus, PSP can appreciably increase the secretion of IL-2 in mice.

2.2. The Effect of PSP on the Immunological Function of Mice After Injection of Cyclophosphamide

2.2.1. The effect of PSP on the white blood cells (WBC) of mice injected with cyclophosphamide. 144 Kunming breed mice were divided randomly into normal, negative (physiological saline) and positive (batyl alcohol) control groups, and PSP high, medium and low dosage groups. With the exception of the control group, the mice were given PSP either orally or by intraperitoneal injection once daily for 8 days. On the fifth day, the mice were injected with cyclophosphamide (100mg/kg). On the eighth day, one hour after administration of the drug, blood was taken from the amimals' tail and the number of white blood cells counted under a microscope.

Table 5 shows that the number of WBC's in mice injected with cyclophosphamide was clearly less than the numbers found in the normal group. The number of WBC's (x10^3/mm^3) fell from 116

TABLE 4. The effect of PSP on the production of IL-2 by mice.

Degree of dilution	Physiological saline group	IL-2 activity (^{3}H-thymidine activity) dpm($\bar{X}$±SD)	
		PSP group	IL-2 group (86µg/ml)
1:6	39155±8655	51639±1090*	138310±16220
1:18	24067±3502	58221±7973*	58343±6433
1:54	12054±679	27741±3322*	16256±9807
1:162	23483±911	7933±248*	1757±270

As compared with physiological saline group, P<0.01.

TABLE 5. The effect of PSP on the white blood cells of the mice after injection with cyclophosphamide*.

Route	Group	Dose	Number of animals	Number of WBC ($\bar{X}$±SD,10^3/mm^3)
PO	cyc*+physiological saline	0.1ml/10g	12	41.75±13.88
	cyc+PSP	1.27g/kg	12	66.58±5.48#
	cyc+PSP	2.25g/kg	12	69.58±21.36#
	cyc+PSP	4.00g/kg	12	74.83±19.72#
	cyc+batyl alcohol	200mg/ kg	12	90.50±22.30#
IP	cyc*+physiological saline	0.1ml/10g	12	66.00±12.20
	cyc+PSP	100g/kg	12	73.08±10.98#
	cyc+PSP	200mg/kg	12	80.67±9.21#
	cyc+PSP	400mg/kg	9	86.44±11.33#
	cyc+batyl alcohol	200mg/ kg	12	87.08±17.87#

*: average WBC of this experiment on normal mice without CYC are 116.33±21.01(10^3/mm^3).
*: cyc=cyclophosphamide; #: compared with cyc+physiological saline; cyc=cyclophosphamide.

to 41 (po) or 66 (ip). However, if the mice were given PSP along with cyclophosphamide, then the drop in WBC count was less. There was a significant difference (P<0.01) between the two groups. Thus, with PSP, the mice are able to resist the lowering effect of cyclophosphamide on the WBC count; that is, PSP can partly restore the drop in WBC's caused by cyclophosphamide injection.

2.2.2. The effect of PSP on IL-2 production in mice injected with cyclophosphamide. Using the IL-2 determination method described above, the amounts of IL-2 produced by groups of mice administered physiological saline, cyclophosphamide, or cyclophosphamide with PSP was compared. The results showed that the amounts of IL-2 produced by the group injected intraperitoneally with cyclophosphamide (25mg/kg) were appreciably lower than the control group (P<0.01). However, if PSP (25mg/kg) was given simultaneously by intraperitoneal injection, then the amounts of IL-2 produced were significantly higher than those produced by the group injected only with cyclophosphamide (P<0.01). This shows that PSP can eliminate the inhibitory effect of cyclophosphamide on IL-2 production (Table 6).

2.2.3. The effect of PSP on the delayed type hypersensitivity (DTH) reaction. 10µl of oil/acetone (1:1) containing 1% dinitrofluorobenzene was applied to the shaved skin of the abdomens (3x3/cm^2) of $C_{57}BL$ mice administered either physiological saline (control), cyclophosphamide (25mg/kg), PSP (25mg/kg), or PSP plus cyclophosphamide. Five days later, a second 10µl aliquot was applied on both sides of the right auricle, but not on the left one. Twenty four hours later, pieces of skin (8 mm in diameter) on both ears were punctured with a perforator and the pieces weighed accurately. The weight difference between the two pieces of skin is an indication of the strength of the DTH reaction.

The result shows that the DTH value of the group of mice injected with cyclophosphamide is significantly lower compared with the physiological saline group (P <0.05). However, the DTH value of the cyclophosphamide plus PSP group is raised appreciably. Compared with the group injected

TABLE 6. The effect of PSP on the secretion of IL-2 by mice injected with cyclophosphamide.

Group	Dose (mg/kg)	Amount of IL-2 (^{3}H-TdR dpm)
physiological saline	-	2537±66
cyclophosphamide	25x2 days	1557±430*
PSP	25x5 days	3020±150
cyclophosphamide plus PSP		2374±120#

*: Compared with physiological saline group, P<0.01; #: Compared with cyclophosphamide group, P<0.01.

only with cyclophosphamide, the P value is less than 0.05 (Table 7). Thus, it can be seen that PSP restores the DTH reaction inhibited by cyclophosphamide.

2.3. The Effect of PSP on the Immunological System of Tumor Bearing Animals

2.3.1. Effect on immunological organs-thymus. After C_{57}BL mice were inoculated with sarcoma-180, PSP was administered orally for 5 consecutive days. The mice were anatomized on the sixth day and their livers, thymuses and spleens weighed. The result shows that the weights of the thymuses of mice taking PSP were significantly increased (P<0.05). Thus, it can be seen that PSP can stop the atrophy of the thymuses of tumor-bearing mice (Table 8).

2.3.2. The effect of PSP on the formation of antibody in sarcoma bearing mice. Several C_{57}BL mice were inoculated with S-180 and then sensitized with sheep red blood cells (SRBC). From the next day, PSP (1g/kg) was administered orally consecutively for 5 days. On the 6th day, blood was removed from the vein cluster behind the eye-sockets, and the amount of anti-SRBC antibody in the serum determined and expressed as half values (HC_{50}).

Using rabbit anti-mouse antiserum, the serum IgG and complement C_3 was determined by the single immunodiffusion method, and the serum IgG and complement C_3 calculated quantitatively from a standard curve. The results show that the HC_{50} values, serum IgG and complement C_3 values are all higher than those of sarcoma bearing mice without PSP. Differences in the serum IgG and

TABLE 7. The effect of PSP on the DTH reaction of mice injected with cyclophosphamide.

Group	Dosage (mg/Kg)	DTH (Strength*)	P value
physiological saline	-	11.0±3.4	
PSP	25	13.3±5.1	
cyclophosphamide	25	7.9±2.3	compared with physiological saline group (p<0.05)
PSP + cyclophosphamide	25	13.0±4.1	compared with cyclophosphamide group (p<0.05)

*weight of right ear minus that of left ear

TABLE 8. The effect of PSP on the weight of the thymuses of the sarcoma bearing mice.

group	dosage (mg/kg x number ofdays)	route	weight of the thymus (mg/10g,body weight)
control	-	po	18±3
S-180	-	ip	10±4*
S-180+PSP	1000x5	ip+po	14±4#

*: As compared with the normal control group without being inoculated with sarcoma-180 (P<0.01).
#: As compared with the group inoculated with sarcoma-180 (P<0.05).

complement C_3 are especially obvious. Thus, PSP causes a definite improvement in the function of the specific and nonspecific immunity systems of sarcoma-bearing mice.

3. CLINICAL RESEARCH ON PSP

485 tumor patients were given PSP along with chemo- and radiotherapy. Control tests were made on 211 cases. Of the remaining 274 cases, random groups were selected for forward-expecting and double-blind control tests.

Various kinds of cancer were involved: stomach (162 cases), esophagus (172 cases) and primary pathogenic lung cancer (151 cases). Those patients accepted for treatment were all proved positive by esophagoscope, X-ray and cell pathology for esophagus cancer; by operation, pathology and gastroscope or X-ray and by pathology of the inspection of live cells for stomach cancer; and by operation, pathology or bronchoscope or X-ray and CT diagnosis and pathological inspection of live cells for lung cancer. Karnofsky evaluations were all ≥60 points, and both the hemopicture and the liver and kidney functions were all within the normal range.

Chemo- or radiotherapy plans applied: MF chemotherapy plan for stomach cancer (MMC+5-Fu); MAP plan (MMC+ADM+DDP) for lung cancer; and Co^{60}-γray radio-therapy plan (DT65-70, Gy/6-7 months) for esophagus cancer.

PSP dosage: 3 grams daily; batyl alcohol, 450 mg/day was used for the positive control group.

Period of treatment: one month as a period of treatment, altogether 2 periods.

Items and methods of determination: included clinical symptoms, inspection and determination of indices and quality of life. For clinical symptoms we mainly observed indices of weariness and

TABLE 9. The effect of PSP on the weight of the antibody and complement C_3 of sarcoma-bearing mice.

Group	Dosage (mg/kg x number of days)	Route	Half value of hemolysin (HC_{50})	Serum IgG (μg/μi)	Serum complement C_3 (μg/10μl)
control	-	po	565±59	71±2	14±4
S-180	-	ip	316±100	73±8	18±3
S-180+PSP	1000x5	po	422±55	95±12*	21±1*

Compared with the group inoculated with sarcoma-180 (P<0.01)

weakness, poor appetite, nausea and vomiting, dryness of throat and mouth, vexation and insomnia, spontaneous and night sweating, and pain before and after treatment.

The inspection and determination indices are mainly to determine the changes in hemopicture (WBC and platelets) and immunological function (natural killing cells, interleukin-2 and T-lymphocytes) before and after treatment. The quality of life is usually expressed by body weight and Karnofsky evaluation. The method of determination follows that of Li (1991).

The following statistical tests were used: Bonferroi X^2 test (G test) for qualitative materials; Ridit or U test for serial materials, and t test for paired materials. $P<0.05$ is required for marked standard.

Standards of the effect of treatment: the following 3 indices were used for the comprehensive determination of the effect of the treatment:

A. Clinical symptoms:markedly improved (the value of integrated mark lowered $\geq 2/3$)
B. Test indices: hemopictures and immunological indices are stable or with some improvement ($\geq 1/3$)
C. Quality of life:weight or Karnofsky evaluation $\geq$ positive control group

If all the above 3 indices are fulfilled - marked effect; if 2 indices AB or AC are fulfilled - effective; and if all the 3 indices are unfulfilled - not effective.

3.1 The Effect of PSP on Improving Clinical Symptoms of Tumorous Patients

After chemo- or radiotherapy, the tumorous patients usually possess symptoms of tiredness, weakness, poor appetite, dryness of mouth and throat, pain, vexation, insomnia, palpitation, shortness of breath, spontaneous and night sweating, leanness, nausea, vomiting,etc. After taking PSP, all the above symptoms were lessened (Table 10). Appreciable relief was evident especially in the case of poor appetite, weakness, tiredness, dryness of mouth and throat and pain. This shows that PSP is good for invigorating not only one's spirit and energy but also one's spleen and heart.

TABLE 10. Effect on the improvement of symptoms before and after treatment.

Symptoms	Control		Treatment		G value *
	Total number of cases	Effective number	Total number of cases	Effective number	
Poor appetite	106	37	114	87	40.480
Weakness and tiredness	107	42	125	90	25.603
Dryness of mouth and throat	58	15	78	46	16.454
Pain	69	23	67	43	13.555
Palpitation and insomnia	80	20	91	37	5.203
Being short of breath	69	26	75	41	5.000
Spontaneous and night sweat	43	12	56	26	4.042
Leanness	62	9	61	18	3.889
Nausea and vomiting	31	15	44	30	3.368

* According to the 9 tests of Bonferroi X^2: $P=0.05$, $X^2(G)=7.689$.

3.2. The Effect of PSP on the Improvement of the Quality of Life of Tumorous Patients

We investigated the effect of PSP on the quality of life of the patients before and after treatment according to body weight and Karnofsky's appraisal value. The results show that the number of cases exhibiting increased or steady weight, and of raised or steady Karnofsky's marks, were significantly higher than among the control group. ($P<0.01$) (Table 11).

3.3. The Effect of PSP on Improving the Immunological Function of Tumor Patients

The analysis determined the changes in the activities of natural killing cells, the amount of the IL-2 of WBC. and the ratio values of CD_4^+/CD_8^+ of T-lymphocytes before and after treatment. The results show that the above-mentioned indices of the test group were all improved. That is, the number of cases of increased NK cell activity, and of increased IL-2 and CD_4^+/CD_8^+ ratio, were all more than observed in the control group. This shows that PSP has a definite effect on the host's ability to resist immunological inhibition due to chemo- and radiotherapy.

3.4. The Effect of PSP on the Change of Blood Picture of Patients Undergoing Chemo- and Radiotherapy

One of the toxic side-effects of chemo- and radiotherapy is that WBC and platelet counts, and hemoglobin levels, are appreciably lowered. Thus, during the process of chemo -and radiotherapy for the treatment of cancers, it is necessary for the patients to take batyl alcohol in order to prevent worsening of the hemopicture.

We replaced batyl alcohol with PSP, observed the changes in the hemopicture of patients after

TABLE 11. The weights of tumor patients and the Karnofsky evaluation condition after treatment.

Item	Group	Total No.	Raised No. %	Steady No. %	Lowered No. %	U value
body weight	control	135	31 22.9	58 42.9	46 34.1	Test group as compared with control group U=3.185 P=0.0041
	treatment	139	52 37.4	60 43.2	27 19.4	
	PSP control	211	78 37.0	100 47.3	33 15.6	
Karnofsky evaluation	control	135	40 29.6	81 60.0	14 10.4	Test group as compared with control group U=2.957 P=0.0031
	treatment	139	62 44.6	72 51.8	5 3.6	
	PSP control	211	44 20.9	163 77.2	4 1.9	

Body weight: an increase or decrease of 1 kg or more regarded as "raised", an increase or decrease of less than 1 kg as "steady" and a decrease of more than 1 kg as "lowered".
Karnofsky's evaluation: an increase or decrease of 10 or more points regarded as "lowered" or "raised" and the rest regarded as "steady".

TABLE 12. Determination of NK cell activity after treatment with PSP.

Group	No. of cases	No. of raised cases	No. of lowered cases	Rate of increase %
control	135	57	78	42.22
treatment	138	89	49	64.49
PSP control	206	142	42	68.93

Note: comparison between the control and treatment group: X^2=13.6144; P=0.000199.

TABLE 13. Determination of IL-2 levels before and after treatment with PSP.

Group	No. of cases	d±sd	t value	P value
control	81	-0.91±23.56	0.3467	>0.05
treatment	88	7.96±16.85	4.4330	<0.001

Note: apply t test for the paired weighing of the materials (differential statistics) df is n-1.

TABLE 14. Determination of CD_4^+/CD_8^+ ratio values before and after treatment with PSP.

Group	Total No. of cases	No. of raised cases	No. of steady cases	No. of lowered cases
control	133	62	3	68
treatment	133	89	7	37
PSP control	211	133	12	66

Note: comparison between control and treatment group: U=3.158; P=0.006.

treatment, and compared them. The results show that the numbers of WBC and platelets, and hemoglobin levels, all corresponding to those values observed with batyl alcohol (Tables 15,16 and 17). They show that PSP has a definite improving function in preventing the worsening of the hemopicture.

4. DISCUSSION

The pharmacological research described above proves that PSP has the obvious function of fostering the positive forces of one's body. Not only can it strengthen the immunological function of the normal organism but it also adjusts immunological inhibition, caused by tumor-bearing or the use of chemotherapeutic drugs, back to the normal state. The philosophy of Chinese traditional medicine is to foster the positive forces and remove the evil ones in order to effect the cure. "Nei Jin",

TABLE 15. Determination of WBC counts after treatment with PSP.

Group	No. of cases	≥4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
control	135	97	25	12	1	0
treatment	139	105	23	10	1	0
PSP control	211	188	12	11	0	0

Note: the ratio between treatment and control group: U=0.7057; P=0.48.

TABLE 16. Determination of hemoglobin levels after treatment with PSP.

Group	No. of cases	≥11.0	9.5-10.9	8.0-9.4	6.5-7.9	<6.5
control	134	82	36	15	1	0
treatment	139	97	26	15	1	0
PSP control	211	16	34	13	1	0

Note: the ratios between treatment and control group: U=1.3139; P=0.2516.

TABLE 17. Determination of the numbers of platelets after treatment with PSP.

Group	No. of cases	≥10.0	7.5-9.9	5.0-7.4	2.5-4.9	<2.5
control	135	103	22	9	1	0
treatment	139	114	24	1	0	0
PSP control	211	167	37	6	1	0

Note: the ratio between treatment and control group: U= 1.3948; P=0.1633.

the classical Chinese medical compendium states, "with positive forces inside one's body, the evil negative forces can't interfere with them and, with the victory of the positive, the evil ones will disappear". Fostering the positive will surely remove the evil forces in our bodies. Our tumor-inhibiting tests also prove that PSP can inhibit sarcoma-180, Ehrlich ascetic tumor, p388 leukemia, human lung adenocarcinoma, monocytic leukemia, histiocytic lymphoma, stomach, liver, nose and throat cancers (Yang *et al.*, 1992).

In the sarcoma-180 experiments, we devised a proof by contradiction; that was to give anti-lymphocyte serum (ALS) while using PSP. The result showed that if only PSP (50mg/kg ip x 10) is used, the tumor inhibition rate is 44%, whereas if PSP is used together with ALS (0.1 ml x 10), then the tumor inhibition rate falls to 0%. That is to say, the tumor inhibition function of PSP on sarcoma-180 will be cancelled by ALS. This suggests that the removal of the evil forces (inhibition of sarcoma-180) by PSP is related to the fostering of positive forces (activation of the immunological function of the organism) (Zhou *et al.*, 1988).

According to the above pharmacological experiments and modern tumor immunology research, we consider that the tumor inhibition effects of PSP are brought about mainly through the following

ways (Takemaru, 1991; Takashi, 1992):

PSP→complement C_3→activate macrophages→inhibit cancer cells

PSP→help T-lymphocytes (CD_4^+)→T-killer cells→inhibit cancer cells

PSP→helpT-lymphocytes (CD_4^+)→B-lymphocytes→antibody→inhibit cancer cells

PSP→help T-lymphocytes (CD_4^+→Interleukin-2→LAKcells→inhibit cancer cells

PSP→natural killing cells→inhibit cancer cells

We consider that the above are perhaps the basic mechanisms for PSP to foster the positive forces and remove the negative ones.

The results of the clinical research correspond to the pharmacological experiments. The results of PSP application to 485 cases of stomach, lung and esophagus cancers clearly show that PSP can lower the toxic and side-effects of chemo -and radiotherapy, lessen the seriousness of the symptoms, stabilize the immunological functions and raise the quality of life. The Prince of Wales Hospital in Hongkong applied PSP in cases of breast cancer and discovered that it can appreciably improve the drop in WBC levels due to the use of chemotherapeutic medicines (cyclophosphamide, 4' epidoxorubicin). Chemotherapeutic drugs will decrease the number of WBC's from 6.96 to 5.05×10^3/mm^3 ($P<0.01$). However, in the group of patients administered PSP, the numbers of WBC's are stabilized at $6.82\text{-}7.02 \times 10^3$/mm^3 ($P>0.05$) (Shiu *et al.*, 1992).

Lessening the seriousness of clinical symptoms, and stabilizing and raising the various pharmacological indices will necessarily raise the effects of treatment and prolong the patients' lives. Clinical tests indicated that, after taking PSP together with chemotherapy, the curative rate in patients with esophagus cancer was raised from 42% in the control group to 72%. The one year survival rate was raised from 40.2% to 51.2% (Liu, 1991; Yao *et al.*, 1992).

5. SUMMARY

The protein bound polysaccharide, PSP, extracted from the mycelia of Yun Zhi Cov-1 is a new BRM substance. Pharmacological and clinical research prove that PSP has the miraculous effect of fostering the positive, and removing the negative, forces of our body. Though the cancer-killing power of BRM drugs is not so powerful as that of chemo- and radiotherapy, they can clearly eliminate the immunosuppression function associated with chemo- and radiotherapy and thereby raise the quality of life. Thus, BRM's have a real value in the comprehensive treatment of tumors. We sincerely hope that BRM substances in Chinese traditional medicine will make greater contributions to the sacred struggle of man's victory over cancer.

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