The Use of Mushroom Glucans and Proteoglycans in Cancer Treatment

by Parris M. Kidd, PhD

Abstract
Immunoceuticals can be considered as substances having immunotherapeutic efficacy when taken orally. More than 50 mushroom species have yielded potential immunoceuticals that exhibit anticancer activity *in vitro* or in animal models and of these, six have been investigated in human cancers. All are non-toxic and very well tolerated. Lentinan and schizophyllan have little oral activity. Active Hexose Correlated Compound (AHCC) is poorly defined but has shown early clinical promise. Maitake D-Fraction has limited proof of clinical efficacy to date, but controlled research is underway. Two proteoglycans from *Coriolus versicolor* – PSK (Polysaccharide-K) and PSP (Polysaccharide-Peptide) – have demonstrated the most promise. In Japanese trials since 1970, PSK significantly extended survival at five years or beyond in cancers of the stomach, colon-rectum, esophagus, nasopharynx, and lung (non-small cell types), and in a HLA B40-positive breast cancer subset. PSP was subjected to Phase II and Phase III trials in China. In double-blind trials, PSP significantly extended five-year survival in esophageal cancer. PSP significantly improved quality of life, provided substantial pain relief, and enhanced immune status in 70-97 percent of patients with cancers of the stomach, esophagus, lung, ovary, and cervix. PSK and PSP boosted immune cell production, ameliorated chemotherapy symptoms, and enhanced tumor infiltration by dendritic and cytotoxic T-cells. Their extremely high tolerability, proven benefits to survival and quality of life, and compatibility with chemotherapy and radiation therapy makes them well suited for cancer management regimens.
(*Altern Med Rev* 2000;5(1):4-27)

Introduction

As the new millennium dawns, humanity continues to strive for longer lifespan and better quality of life. But the disease of cancer continues to be the scourge of humanity; being a leading cause of early death, and resistant to therapies aimed at its eradication. Now another dimension of anticancer therapy is available – immunotherapy, a means by which the body's immune defenses, beaten down by the cancer and by toxic therapies used against the cancer, can be revitalized to carry out their natural functions of eliminating abnormal tissues from the body. The tools for immunotherapy are naturally-occurring substances, herein christened immunoceuticals, which can be included in the general category of nutraceuticals, or dietary supplements.

Parris Kidd, PhD (Cell biology, University of California at Berkeley); Contributing Editor, Alternative Medicine Review; Health educator and biomedical consultant to the supplement industry.
Correspondence address: 535 Pierce St. Suite 209 Albany, CA 94706.

Mushrooms have been recognized for their medicinal properties for five millennia.[1] It was not until the last one-third of the past century that technology was capable of biochemically dissecting traditional medicinal mushrooms and isolating their most active anticancer constituents. Once concentrates of such substances became reliably available, they were screened in animal models of cancer prior to appropriate anticancer application in humans. Some of these mushroom-derived substances were found to be highly potent immune system enhancers, potentiating human immunity against cancer more effectively than other anticancer agents. This review focuses on mushroom immunoceuticals; preparations from mushrooms which have been systematically investigated for their oral anticancer action.

Mushroom Immunoceuticals – An Overview

Immunoceuticals isolated from more than 30 mushroom species have shown anticancer action in animals.[2] Only a handful have been taken to the next step: objective clinical assessment for anticancer potential in humans. Of these relative few, all are chemically ß-D-glucan in nature (i.e., linear polymers of d-glucose with other monosaccharides) or ß-D-glucans linked to proteins (so-called polysaccharide-peptides, more formally termed "proteoglycans"– see Figure 1). As a rule, the protein-linked glucans

Figure 1. The molecular plan of a mushroom proteoglycan. The central, linear polypeptide chain has multiple, branched chains of poly-beta-D-glucans attached.
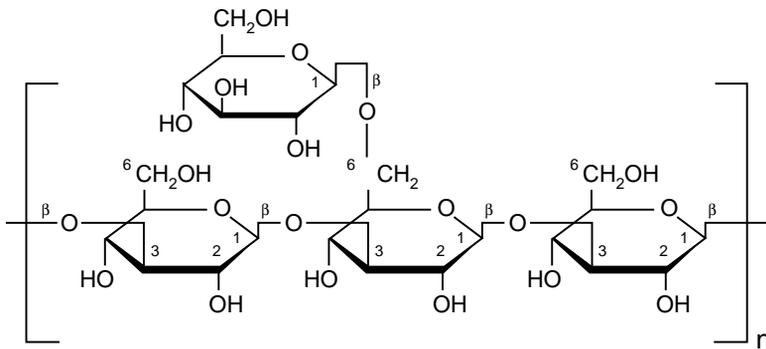Modified from Molecular Biology of the Cell.[7]

Glucan Chains

Core Proteins or Polypeptides
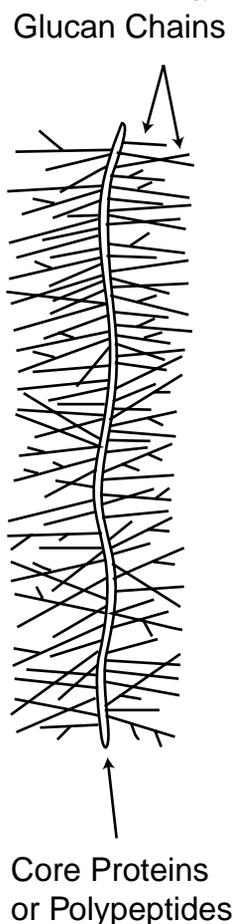
have greater immuno-potentiation activity than the corresponding free glucans.[3]

The basic ß-D-glucan is a repeating structure, with its D-glucose molecules joined together in linear chains by beta-bonds (ß). These can extend from the carbon 1 of one saccharide ring to the carbon 3 of the next (ß1-3), from carbon 1 to carbon 4 (ß1-4), or from carbon 1 to carbon 6 (ß1-6). Most often there is a main chain which is either ß1-3, ß1-4, or mixed ß1-3, ß1-4 with ß1-6 side chains. The basic repeating structure of a ß1-3 glucan with ß1-6 side chains is shown in Figures 2a and 2b. Hetero-ß-D-glucans, i.e., linear polymers of glucose with other D-monosaccharides, can have anticancer activity, but alpha-D-glucans from mushrooms usually lack anticancer activity.[6]

Six mushroom preparations have shown clinically significant efficacy against human cancers: lentinan, schizophyllan, Active Hexose Correlated Compound (AHCC), Maitake D-Fraction, Polysaccharide-K, and Polysaccharide-P. Since lentinan and schizophyllan have limited oral bioavailability, and therefore fail to meet the definition of immunoceutical, they will only be given a cursory review. AHCC and Maitake D-Fraction are still in the early stages of investigation. The remaining two have been subjected to in-depth application against cancers in humans.

Figure 2a. Primary molecular diagram of mushroom beta-D-glucans. From Yanaki et al[4]

Lentinan from Shiitake

Lentinan, produced from the Shiitake mushroom *Lentinus edodes*, is a ß1-3, ß1-6 D-glucan. Glucan preparations are always heterogeneous in molecular weight, but lentinan is particularly large, on the order of 400,000-1,000,000 daltons. Its oral bioavailability is reportedly limited; thus, it has been routinely administered intravenously. Open-label clinical studies indicate lentinan can prolong life in patients with gastric or colorectal cancer, as reviewed recently by Borchers et al.[1] Lentinan has been satisfactorily proven to potentiate human immunity.[1,2,8]

Schizophyllan (SPG, Sonifilan, Sizofiran, Sizofilan)

Schizophyllan, from *Schizophyllum commune,* is another ß1-3, ß1-6 D-glucan too large for effective oral administration. Its molecular weight ranges around 450,000 daltons and it is usually administered by intramuscular injection. Schizophyllan was found rather ineffective against gastric cancer, but extended survival time in patients with head and neck cancer.[1,9] In cervical cancer, schizophyllan prolonged survival and time to recurrence for stage II cases but not stage III,[10-12] and showed added effectiveness when injected directly into the tumor mass.[13]

Active Hexose Correlated Compound (AHCC)

Active Hexose Correlated Compound (AHCC) is a proprietary extract prepared from co-cultured mycelia of several species of Basidiomycete mushrooms, including shiitake (*Lentinus edodes*). Mushroom sources and details of the methods of preparation have not been fully disclosed.[14] The extract is made using hot water following an enzyme pretreatment; it contains polysaccharides, amino acids, and minerals, and is orally bioavailable. According to its manufacturers, the glucans in AHCC have low molecular weight (around 5,000 daltons) and are of the alpha-1,3 type.[14] Both these attributes are peculiar for immunoactive mushroom glucans – typically such low-molecular weight material is inactive, and as a rule the alpha-glucans have minimal immuno-potentiating activity;
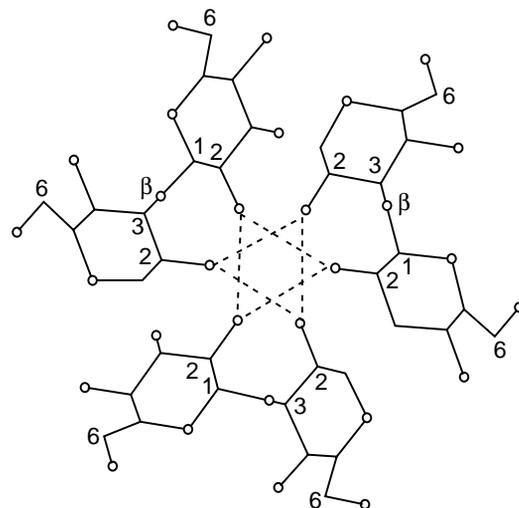

Figure 2b. Higher-level molecular diagram of mushroom beta-D-glucans. From Bluhm[5]

yet animal research and preliminary human studies indicate AHCC has anticancer efficacy.

Beginning in 1992, Kamiyama conducted a trial in Japan to evaluate the preventive effect of AHCC against recurrence of hepatocellular carcinoma following surgical resection.[15] After surgery, 126 patients were separated into two groups: 44 patients were administered AHCC, 3 grams per day orally, while the other 82 served as controls. Unfortunately, the outcome of this trial is published to date only in abstract form. The investigators reported that after one year the AHCC group showed a significantly higher survival rate than the control group, as well as significant lowering of certain tumor markers in the serum.

In another published abstract based on this same study, Kamiyama et al stated liver tumor recurrence was not lower in the AHCC group, although the survival rate was higher.[16] They claimed AHCC-treated patients who experienced improved survival were positive for hepatitis C; and patients who were either hepatitis B-positive or negative for hepatitis viruses did not experience better survival rates. They reported the AHCC-treated patients also had significantly decreased levels of liver damage markers SGOT and SGPT. Among these patients, significant improvements were noted in lymphocyte and red cell counts, and in appetite and anemia.[14] In four cases where cirrhosis was also present, ascites developed and was successfully treated with 3-6 grams/day of AHCC.

The AHCC Research Association was formed in Japan in 1996 to foster the development of AHCC as an anticancer therapy. In their circulating abstracts[14] they report on other preliminary studies with AHCC against cancer. They state that of 300 cancer patients administered AHCC, 58 were effectively treated, with 46 showing complete or partial regression and 12 experiencing no change of tumor size. Among these 58 cases were cancers of the lung, breast, stomach, esophagus, colon, liver, and several other sites. It is not possible from the limited data to calculate relative efficacies, improvements in survival or recurrence, or quality of life benefit for any of these cancers. Research on AHCC is at a comparatively early stage, but its declared efficacy against liver cancer warrants further investigation.

Maitake D-Fraction

Maitake D-Fraction is a mixed ß-D-glucan fraction prepared from the maitake mushroom (*Grifola frondosa*) and is orally bioavailable (see Jones[17] for an overall review). Maitake has been used as food in Japan for hundreds of years, in amounts up to several hundred grams per day, and its safety is established. A hot-water extract from the fruiting body of the mushroom was found to be highly potent against human cancer cells in culture. Subsequently, the D-fraction was prepared from the crude hot-water fraction by deproteination.[17]

Maitake D-Fraction contains mainly ß-D-glucan material with 1-6 main chains and 1-4 branchings, and the more common 1-3 main chains and 1-6 branchings.[18] This fraction also is highly active *in vitro* and in animal models of cancer, although activity in these experimental systems does not necessarily predict anticancer efficacy in humans.

Maitake D-Fraction has been used in a few exploratory studies in cancer patients.[17] In 1994, a group from China published in abstract form their findings from a pilot study on 63 cancer patients. They reported the total effective rate against solid tumors at higher than 95 percent, and the effective rate against leukemia higher than 90 percent.[17] Unfortunately, the concentration of the extract used was not disclosed.

In 1995, Nanba published an informal summary of an open-label, non-randomized study conducted in Japan.[19] In this study, 165 patients with various cancers, many with

advanced progression and some refusing chemotherapy, were treated with D-Fraction plus tablets of dried crude extract of maitake. Dosages varied from patient to patient, with D-fraction doses ranging from 35-100 mg per day and crude mushroom extract ranging from 4-6 grams. Symptomatic improvements or regression were claimed for approximately 73 percent of the breast cases and 67 percent of the lung cases. Of the liver cancer cases, 47 percent were said to have responded, which jumped to 73 percent when chemotherapy was also utilized. In contrast to the incredible response rates claimed in the Chinese study, in the Japanese study less than 50 percent of the leukemias and cancers of the prostate, brain, stomach, and bone seemed to respond. The disease subgroups were small, however, the largest number of cases studied being 19 (liver cancer, with chemotherapy). According to Nanba, 83 percent of the patients experienced lessening of pain, and 90 percent experienced improvement of chemotherapy-related symptoms such as vomiting, nausea, reduced appetite, hair loss, intestinal bleeding, and lowered white cell count.

These claims of benefit from Maitake D-fraction are encouraging. In the absence of adequate peer review and especially without access to the primary data, however, it is difficult to assign meaning to them. Nonetheless, several U.S. physicians have reported good results with Maitake D-fraction in their practices, and an Investigative New Drug approval was obtained in 1998 to begin a Phase II pilot study with this material on patients with advanced breast and prostate cancer.[20]

Proteoglycans from *Coriolus versicolor*

The mushroom-derived "polysaccharide-peptides," or proteoglycans, are polypeptide chains or small proteins to which polysaccharide ß-D-glucan chains are stably attached. Up to this point, PSK and PSP are the only two proteoglycans systematically investigated in human cancers.

Coriolus versicolor (formerly *Trametes versicolor, Polyporus versicolor*) is a mushroom which grows on tree trunks and belongs to the more-advanced Basidiomycetes class of fungi. This mushroom has long been treasured in the East; in Japan it is known as *kawaratake* ("mushroom by the river bank"), and in China it is called *Yun Zhi* or "cloud fungus." In Japan around 1965 a chemical engineer investigated *Coriolus versicolor* for its anticancer constituents after observing his neighbor's life-threatening cancer was cured after taking Yun Zhi. This led to the discovery of PSK (Polysaccharide-K).[21] The closely-related PSP (Polysaccharide-Peptide) was first isolated in China some time later, around 1983.[22]

PSK Constituents

PSK is prepared from strain CM-101 of *Coriolus versicolor* by water extraction and salting out. It is approximately 62-percent polysaccharide and 38-percent protein, although the content of both can vary. The glucan portion of PSK consists of a ß1-4 main chain and ß1-3 side chains, with ß1-6 side chains that bond to a polypeptide moiety through O- or N-glycosidic bonds. The polypeptide portion is relatively rich in aspartic, glutamic, and other acidic amino acids. PSK is a set of molecules whose molecular weight ranges from 94,000 to 100,000 daltons, and is bioavailable by the oral route.[23] Studies with C14-labeled PSK in mice confirmed its full molecular spectrum is absorbed within 24 hours following administration. Conventional toxicological assessments indicate PSK is non-toxic: its oral LD50 is low and no abnormalities have been observed in subacute and chronic toxicity tests.

PSK Clinical Trials

The first clinical trial research with PSK began around 1970. Decades of clinical

Table 1. PSK: Controlled Trials in Stomach Cancer

Cancer type	Authors	Subjects	Outcome
Stomach Stage IV w/inv., metas.	Kaibara et al, 1976[24] Surgery w/MMC +/- PSK w/chemo	66	PSK w/chemo doubled 2-yr survival (p<0.05), incl. pts w/ invasion-metastasis
Stomach all stages	Fujimoto et al, 1979[25] Surgery +/- PSK w/ chemo	230	PSK w/chemo extended survival of one subset (p<0.001) but not poor immune responders
Stomach Stages I-IV	Hattori et al, 1979[26] Surgery w/MMC +chemo +/-PSK	110	PSK w/chemo improved 3-yr survival (poor stat. analysis) PSK no deaths stage III 2 yrs
Stomach, Adv. w/inv., metas.	Kodama et al, 1982[27] Surgery w/MMC +/- PSK w/chemo	450	PSK w/chemo doubled 5-yr survival (p<0.01)
Stomach Stage III DOUBLE-BLIND	Kondo and Torisu, 1985[28] Surgery/no chemo +/-PSK	144	PSK extended disease-free period (no p-value given); enhanced immunity (p<0.05)
Stomach Stages I-IV	Mitomi, Ogoshi, 1986[29] Surgery + chemo +/-PSK	168	PSK extended 5-yr survival (p<0.05)
Stomach, Adv. w/inv., metas.	Niimoto et al, 1988[30] Surgery w/MMC +/-chemo +/-PSK	579	PSK extended 5-yr survival (p<0.05); pre-op immunity predicted PSK benefit
Stomach, Adv. w/inv., metas.	Maehara et al, 1990[30] Surgery +/- PSK w/chemo	255	PSK w/chemo extended 15-yr survival (p<0.035)
Stomach Stage III	Tsujitani et al, 1992[34] Surgery + MMC + chemo +/-PSK	53	PSK extended 5-yr survival (p<0.05)
Stomach, I-IV	Nakazato et al, 1994[32] Surgery + chemo +/-PSK	253	PSK extended 5-yr survival (p<0.05), disease-free period (p<0.04)

MMC=mitomycin-C; chemo=5-fluorouracil (5-FU) or derivative, long-term, sometimes combined with other agents; PSK=Polysaccharide-K, at 3-6g/day for 1 year or longer. See individual references for details.

Mushroom Glucans & Proteoglycans

experience indicate PSK is very gentle on cancer patients, its only significant side-effect being occasional darkening of the fingernails. To date, PSK is most clinically indicated for cancers of the stomach, esophagus, nasopharynx, colon, rectum, and lung (see Tables 1 and 2). It has also shown promise in a subset of breast cancers.

PSK and Stomach Cancer

Stomach cancer continues to inflict major mortality in Japan and has been the object of more clinical trials with PSK than any other cancer. Beginning in 1970, Kaibara and his colleagues at Kyushu University in Fukuoka, Japan, began adding PSK immunotherapy to their existing chemotherapy protocols.[24] Hoping to achieve a clearcut result after two years, they chose to study patients with advanced (Stage IV) cases with invasion and metastasis, since few such patients survive an additional two years. They first performed conventional surgical resection, administering Mitomycin-C (MMC) beginning on the day of surgery. The patients were then put on a long-term chemotherapy regimen of Futraful, a 5-fluorouracil (5-FU) derivative, with periodic MMC treatments. PSK was added at 3 grams per day orally. The overall combination regimen was named "chemoimmunotherapy." This group was retrospectively compared against a patient group treated in earlier years with surgery and MMC, but not with the chemoimmunotherapy regimen.

Kaibara's group found survival was better in the chemoimmuno- group by more than double (34% vs 11%, p<0.05) after two years.[24] This finding was later supported by a similar trial conducted by Fujimoto and associates at Chiba University.[25] In addition, Hattori's group at Hiroshima University did a trial in which they also monitored immune competence using skin DTH (delayed-type-hypersensitivity) reactions and lymphocyte blastogenesis following induction by mitogens.[26] Treatment after surgery with the combination of PSK as immunotherapeutic (6 grams/day) and 5-FU as chemotherapeutic was again found more effective for long-term survival of stomach cancer patients compared to treatment with MMC only after surgery. In this trial, the combination of PSK with 5-FU very likely increased three-year survival. Although the statistical analysis was flawed, survival data clearly indicated benefit after the first year, and among Stage III patients taking the combination all survived greater than two years. PSK showed a tendency toward protecting against the immunosuppression that typically accompanies surgery and long-term chemotherapy. By the early 1980s, once more reinforced by the results of Kodama et al,[27] the use of PSK as the immuno-component of chemoimmunotherapy consistently doubled the two-year survival rate for stomach cancer in Japan.

In a 1985 double-blind trial with PSK in stomach cancer, patients with Stage III stomach cancer were treated with PSK or a placebo post-surgery, without the use of chemotherapy.[28] PSK significantly extended the disease-free period over 80 months, although survival rate was not significantly extended. The investigators criticized their decision to administer PSK so tentatively: 3 grams/day for the first two months, 2 grams/day for up to 14 months, then 1 gram/day thereafter for the remainder of the trial. They speculated their results would have been better had PSK been given at 3 grams/day for the duration of the trial. The only statistically significant adverse effect from PSK was darkened pigmentation of the fingernails, occurring in four of 77 patients. After two months on PSK in this trial, patient immunocompetence was significantly improved, as judged by increased DTH (delayed-type hypersensitivity) on skin tests and enhanced chemotactic migration of neutrophils. Interestingly, this group also found PSK would improve DTH in aged men who had lowered immunity, but did not have cancer. As the trials progressed it became evident that individuals with very low immunity were less likely to benefit from PSK therapy than were individuals with some degree of remaining immunity.

During the 1980s and 90s, four trials established that PSK improved survival in

Figure 3. Survival rates of stomach cancer patients with marked dendritic cell infiltration (top) or slight infiltration (bottom), given either chemotherapy alone or chemotherapy with PSK (immunochemotherapy). From Tsujitani et al, 1992.[34]
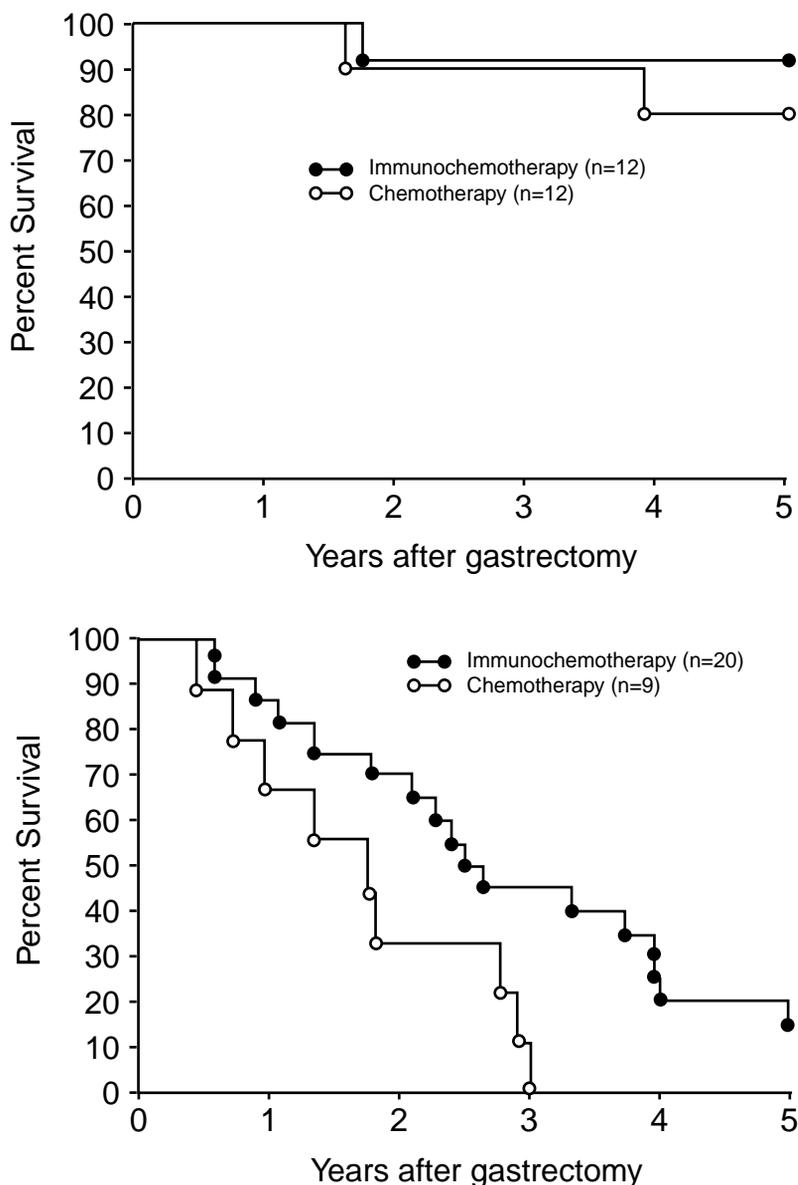
that make it useless to interpret.[33]

A 1986 trial by Mitomi and Ogoshi was the first attempt to separate the PSK-induced increase in stomach cancer survival from the effects of long-term chemotherapy. Significantly better five-year survival was reported with PSK. Two years later, in the Niimoto prospective randomized trial on 579 patients,[30] another direct comparison of long-term chemotherapy versus long-term chemotherapy with PSK also concluded that PSK contributed significantly to five-year survival (p<0.01). Furthermore, patients found to benefit most from PSK were those with invasion and/or metastasis and those with better immune competence prior to surgery, as measured by skin DTH tests.

After Maehara's group showed PSK combined with chemotherapy can improve survival as far as 15 years (see Figure 4a),[31] their group investigated possible connections of PSK-responsiveness with known immunity mechanisms.[34] Tsujitani et al at Kyushu University observed earlier that dendritic cells could infiltrate cancerous stomach lesions in their patients.[34] Further examination of biopsy material revealed that patients who achieved extended survival were those who exhibited the most marked dendritic cell infiltration of their tumors prior to surgery.

stomach cancer patients up to five years, including some patients with advanced Stage III and IV cases with metastasis.[29-32] Another trial conducted during this period, which enrolled more than 5,400 participants, had design flaws

Certain immune cells which resemble macrophages are located in the skin and virtually all other tissues, and very likely act as an early warning system for the body's immune defenses. Having dendritic or finger-like projections, they are called dendritic cells, unless they are present in the skin, where they are termed Langerhans cells. These immune cells often are the first to detect the presence of foreign antigens and initiate an appropriate response against them. These cells first ingest the foreign material, then break it down to smaller pieces. Subsequently they can "present" the antigens to T-cells, with which they habitually interact at close range to cooperatively mount immune responses, including cytotoxic activity against cancerous tissue. Dendritic-killer cell coordinated responses are the prototypical mechanism for tumor cell killing.

Further retrospective examination of tissue samples from 53 patients with Stage III stomach cancer, of whom 20 had received PSK as immunotherapy, demonstrated that among patients manifesting marked tumor infiltration by dendritic cells at the time of surgery, five-year survival was greater than 90 percent; yet PSK did not significantly enhance survival. Among patients with low dendritic cell infiltration, five-year survival was a mere 10 percent. Thus, of nine such patients subjected to conventional chemotherapy without PSK, none survived beyond three years. Of 20 who received the same chemotherapy regimen with PSK, nine (45 percent) were still alive at three years. (see Figure 3) The investigators concluded for stomach cancer patients who show limited dendritic cell infiltration prior to surgery, PSK immunotherapy is likely to significantly increase their chance for long-term survival.

In 1994, *The Lancet* published the findings from a well-designed trial on PSK therapy in the treatment of stomach cancer conducted by the Study Group of Immunochemotherapy with PSK for Gastric Cancer of Japan.[32] Che-motherapy with PSK was compared against chemotherapy without PSK, and PSK was again found to significantly improve both five-year survival and disease-free survival (see Figure 4b). No toxic effects could be observed for PSK, "even after meticulous review of all the patient records.…" Although the exact degree of benefit from PSK was subsequently challenged,[35] this trial has great clinical significance.

PSK and Colorectal Cancer

As its benefits to stomach cancer became established, PSK was assessed for its potential anticancer activity in patients with advanced colorectal cancer. In an eight-year, double-blind trial,[36] 111 patients with colorectal cancer (pathologic stages III and IV, Dukes Stage C) were randomized into two groups, then administered PSK or placebo in decreasing doses over time, as per Kondo and Torisu's earlier gastric cancer study. PSK, 3 grams/day, was given until two months after surgery, followed by 2 grams/day until 24 months, and 1 gram/day thereafter. PSK significantly improved both the eight-year survival rate (to 40% vs. 25%, $p<0.05$) and the disease-free interval (to 25% vs 8%, $p<0.05$).

In 1992, Mitomi et al, in the Cooperative Study Group of Surgical Adjuvant Immunochemotherapy for Cancer of Colon and Rectum, published the results of a large multicenter trial with PSK in colorectal cancer.[37] They recruited 448 patients from 35 institutions in Japan, randomized them into two groups, then put them through surgery and chemotherapy plus or minus PSK. After the third year, PSK had significantly improved survival and the disease-free period in the colon group ($p<0.05$ in both)(see Figure 4c), but not in the rectal cancer group ($p=0.12$).

Table 2. PSK: Controlled Trials in Other Cancers

Cancer Type	Authors	Subjects	Outcome
Colorectal DOUBLE-BLIND	Torisu, Kondo et al, 1990[36] Surgery/no chemo +/-PSK	111	PSK extended 8-yr survival ($p<0.05$), disease-free period ($p<0.05$), enhanced DTH immunity ($p<0.05$)
Colorectal	Mitomi et al, 1992[37] Surgery + chemo +/-PSK	448	PSK extended colon 5-yr survival ($p<0.04$), disease-free period ($p<0.05$); rectal benefits not sig. ($p=0.1$)
Esophageal	Ogoshi et al, 1995[39] Surgery + radiother. (RT) +/- chemother. (CT) +/- PSK	158	PSK extended 5-yr survival post- surg+RT+CT ($p<0.03$); normalized serum factors
Nasopharyngeal	Go and Chung, 1989[41] Radiotherapy +/- chemother. +/-PSK	34	PSK extended 5-yr survival ($p<0.04$), but not disease-free period
Lung (NSCLC) Stages I-III	Hayakawa et al, 1993[42] Radiother. +/-PSK	185	PSK extended 5-yr survival 2-4x, all stages ($p<0.005$); tumors <5cm, age >70 yrs more benefit ($p<0.04, 0.01$)
Breast, ER+/- Stage II, IIIA post-surgery	Toi et al, 1992[44] MMC +/- Tamoxifen +/- Ftorafur +/- PSK	914	PSK extended survival in ER-neg, non-metas. Stage II ($p<0.002$)
Breast, ER+/- Stage II post-surgery	Morimoto et al, 1996[45] MMC+/- Tamoxifen +/- Ftorafur +/- PSK	889	No evident benefit from PSK
Breast Stages I, II	Iino et al, 1995,[46] 1997[47] FEMP chemotherapy + Levamisole or PSK; compared HLA B40+ vs HLA B40-	227	PSK trend to extended 10-yr survival ($p=0.07$), 10-yr disease-free period ($p=0.1$); HLA B40+ pts. had 100% 10-yr survival ($p<0.05$)
Leukemia/ANLL in remission	Ohno et al, 1984[48]	67	Trend to lengthened remission ($p=0.1$) in pts. with remission >270 days
Leukemia/ALL in remission	Kawa et al, 1991[49]	108	No evident benefit from PSK

PSK and Esophageal Cancer

Pre- and post-operative radiotherapy can improve survival in esophageal cancer. In 1980, Okudaira et al reported on a non-controlled, retrospective analysis of their success with combined radiation, chemotherapy, and immunotherapy in 133 cases.[38] They concluded the addition of immunotherapy to the regimen using either PSK or OK-432 (an immunopotentiator which has undesirable side-effects) significantly improved both one-year and two-year survival.

In the Cooperative Study Group for Esophageal Cancer in Japan, a prospective, randomized, multi-center study of 158 esophageal cancer patients,[39] researchers followed five-year survival and its relationship to alpha 1-anti-chymotrypsin (ACT) and sialic acid (SA) levels. These serum-borne substances are immunosuppressive at high serum levels, but are sometimes lowered by PSK treatment. After undergoing surgery, followed by radiotherapy, patients were randomly assigned to one of four groups. Two groups received chemotherapy, one with and one without PSK; the other two received no chemotherapy, one with and one without PSK.

After all comparisons were complete, patients who received PSK (3 grams/day for three months beginning immediately after surgery) had a significantly better survival rate at five years ($p < 0.03$). Those with abnormally high levels of ACT had poor survival unless they received PSK (26% vs 55%, $p < 0.008$). The same was true for patients with abnormally high SA (31% vs 58%, $p < 0.07$). This shows PSK clearly benefits five-year survival in esophageal cancer and has markedly greater benefit for those patients with pre-operative high ACT or SA. Ogoshi and other members of this group previously reported a similar pattern in patients with gastric cancer.

PSK and Nasopharyngeal Cancer

Conventional treatment of nasopharyngeal carcinoma has involved radiotherapy, sometimes followed by chemotherapy. In a small controlled trial carried out in Taiwan, researchers randomly selected 34 patients who had received radiotherapy, and administered to 14 of the patients various forms of chemotherapy, using cisplatinum, 5-fluorouracil, methotrexate, and vincristine. Once this primary therapy was completed (radiation or radiation plus chemo-), the entire group was randomized to receive PSK (3 grams per day, for up to two years) or not. As shown in Figure 4d, the PSK group showed significantly extended survival at five years (28% compared to 15% for controls, $p = 0.04$). [41]

PSK and Lung Cancer

In 1977, Hayakawa and colleagues at the Gunma University School of Medicine in Japan began giving PSK to non-small-cell lung cancer patients post-radiotherapy.[42] After establishing radiotherapy was only marginally effective in tumors larger than 2 cm in diameter, they added immune system potentiation to the regimen. One-hundred-eighty-five patients with epidermoid carcinoma, adenocarcinoma, or large-cell carcinoma, of severity up to stage IIIB, were enrolled. Each patient received radiation therapy 6-7 weeks. Sixty-two were subsequently randomly selected to receive PSK 3 grams daily, in repeating cycles of two weeks on and two weeks off. After five years, almost four times more of the patients treated with PSK were alive (27% compared to 7% for those not given PSK, $p < 0.005$) (see Figure 4e).

The benefit to lung cancer patients from PSK in this study is clinically significant in that more-advanced patients with stage III disease who received PSK had a better prognosis than stage I and II patients who did not receive PSK. Furthermore, this trial also demonstrated PSK given in addition to

radiotherapy was particularly helpful for older patients (>70 years, p<0.007) and patients with smaller primary tumors (£ 5 cm diameter, p<0.04). When disease stage was factored out, patients who had higher Karnovsky performance scores prior to receiving PSK also had better survival (p<0.02), suggesting the better-conditioned lung cancer patient stands to benefit more from PSK.

PSK Selective Effectiveness Against Breast Cancer

As early as 1984, Sugimachi's group at Kyushu University published a retrospective analysis of breast cancer patients with recurrent disease, all subjected to "surgical hormone therapy" (total ovary and partial adrenal gland removal). Some patients then received chemotherapy with or without PSK immunotherapy.[43] The earliest-treated group (1961-1969) received only surgical hormone therapy and served as controls. A later group (1970-1976) received mitomycin-C immediately after surgery. An even later group (1970-1981) received long-term combination chemotherapy along with PSK immunotherapy. The survival rate after recurrence was significantly extended by the immunochemotherapy, in comparison to the other two groups. The value of this type of study is limited because the patient groups are drawn from different populations; nonetheless, the findings are marked and support the use of PSK in breast cancer.

In 1992, a large randomized trial evaluated tamoxifen as an addition to the then-conventional chemotherapy, and factored in PSK (3 grams daily for two years) as the immunotherapy arm. This trial involved 914 patients who were sub-analyzed by: (1) estrogen receptor-positive or negative status; (2) extent of metastatic lymph node involvement; and (3) classic cancer stage (Stages I-IV). In-depth analysis revealed PSK significantly extended survival in ER-negative, Stage IIA T2N1 patients without lymph node involvement. This

limited finding was later contradicted by Morimoto's group,[45] who also did a large trial and found no statistical evidence of benefit from PSK.

This seeming paradox may have been resolved by Iino et al, working at Japan's Gunma University.[46,47] Their 1995 trial on breast cancer patients with vascular invasion found strong statistical trends for extended 10-year survival with PSK use (p=0.07), and extended disease-free period (p=0.1). Their data suggested clinical effectiveness, yet the statistics fell short of formal verification. Knowing that HLA B40 antigen status had been linked to likelihood of survival with breast cancer, the researchers compared their B40-positive patients treated with PSK against B40-negatives. After tissue typing and other requisite technical protocols, the researchers established the B40-positive patients who were treated with PSK (3 grams daily, two one-month courses each year) in addition to chemotherapy had 100-percent survival after 10 years,[47] as shown in Figure 4f. The statistical significance compared to the no-PSK chemotherapy group was clear (p<0.05); B40-negative patients treated with PSK had approximately 50-percent survival at 10 years, which was not statistically significant. These provocative findings suggest breast cancer patients may well benefit from taking PSK in conjunction with chemotherapy. Patients positive for HLA B40 antigen may derive great benefit from taking PSK; those who are negative may benefit little or not at all.

PSK in Leukemias (ANLL, ALL)

Acute non-lymphocytic leukemia (ANLL) can be forced into initial remission using aggressive chemotherapy, but remission is often short-lived.[48] In a multi-center Japanese trial on 67 patients with ANLL who were initially in remission after combination chemotherapy, patients were randomized to maintenance chemotherapy or maintenance

chemotherapy plus PSK 3 grams per day. Maintenance chemotherapy was terminated at two years and PSK was continued for the study duration. Survival was followed to approximately 4.5 years. The statistical analysis suggested only a trend toward benefit from PSK (p=0.1), which may have been due to the relatively small number of patients initially enrolled and the even smaller number surviving at the end. There was a suggestion from the data plots that for individuals who remained in remission for 270 days or longer, PSK might add a further remission of as much as 418 days. In another study, PSK did not significantly benefit children in remission from acute lymphoblastic leukemia.[49]

PSK Conclusion

While PSK is not a panacea for cancers, it can improve five-year survival in some indications by as much as double, and perhaps extend survival to as much as 15 years (see Figure 4). In some patient subsets, such as HLA B40-positive breast cancer, or in the presence of risk factors such as impaired immunity or high ACT or SA, PSK can be especially life-saving. PSK also helps conserve immune status in the face of toxic challenge by conventional treatments.[88] After a quarter-century of trials indicating PSK can improve cancer survival, the cumulative human findings amount to a recommendation for its inclusion in standard anticancer protocols. With its risks for adverse effects virtually nonexistent, PSK's contribution to the benefit-risk profiles of these protocols can only be positive.

PSP: *Coriolus versicolor* Polysaccharide-P Extract

PSP ("Polysaccharide-P," polysaccharopeptide) is prepared from cultured mycelium of the COV-1 strain of *Coriolus versicolor*.[22,50] PSP may contain as many as four discrete molecules, all of which are likely to be true proteoglycans. Chromatographic and spectral data from infrared nuclear magnetic resonance and proton resonance are consistent with PSP being polypeptide (small protein) moieties with polymeric monosaccharide chains attached.

The polypeptides in PSP resemble those of the closely-related proteoglycan PSK, in that they are enriched with aspartic and glutamic acids.[51] However, PSP differs from PSK in its saccharide makeup, lacking fucose and carrying arabinose and rhamnose. The polysaccharide chains are true beta-glucans: gas chromatography-mass spectrometry disclosed mainly 1-4, 1-2, and 1-3 glucose linkages, together with small amounts of 1-3, 1-4, and 1-6 galactose, 1-3 and 1-6 mannose, and 1-3 and 1-4 arabinose linkages. A few *alpha*-linkages are probably also present. The molecular weight of PSP is approximately 100,000 daltons,[51] and it is routinely delivered orally.

Clinical research with PSP has taken a fast track since it was isolated in 1983 (for a history, see Yang[52]). With Phase I, II, and III human trials now completed, PSP has been proven to be non-toxic,[21,53-55] with marked immunopotentiation capacity sufficient to improve survival rate and quality of life in cancer patients.[21,50] The Phase I trial provided PSP at doses up to 6 grams per day for one month to 16 healthy persons and five breast cancer patients. Appetite increased in a majority of the subjects, and in this and other preliminary trials no evidence was found for serious adverse effects.[56,57] The Phase II[58] and Phase III[59] trials established that PSP benefits patients with stomach, esophageal, and non-small-cell lung cancers, while substantially protecting against the unpleasant effects of both the cancers *per se* and the toxic therapies conventionally employed to treat them.[60,61]

In the Phase II double-blind trial, conducted in 1992 at several hospitals in Shanghai, 274 patients with stomach, esophageal, or lung cancers were dosed with PSP or shark liver oil (batyl alcohol).[62] Patients received

Figure 4a-f. Clinically significant extension of survival by PSK, in various cancers treated also using conventional chemotherapy and/or radiotherapy. Top, left: stomach, 5-year.[32] Top, right: stomach, advanced, with invasion and metastasis, 15-year.[31] Middle, left: colon, 5-year.[37] Middle, right: nasopharyngeal, 5-year.[41] Bottom, left: Breast, stage II, HLA B40-positive, 10-year.[47] Bottom, right: lung (non-small cell), 5-year.[42]
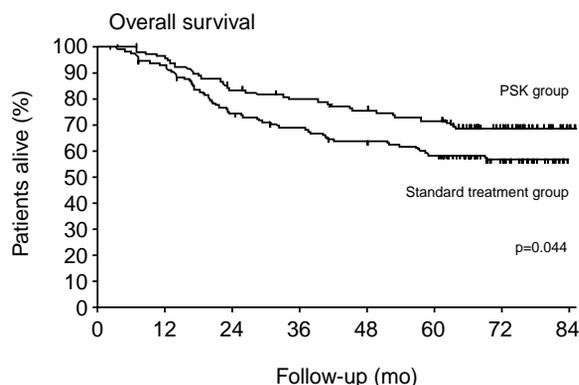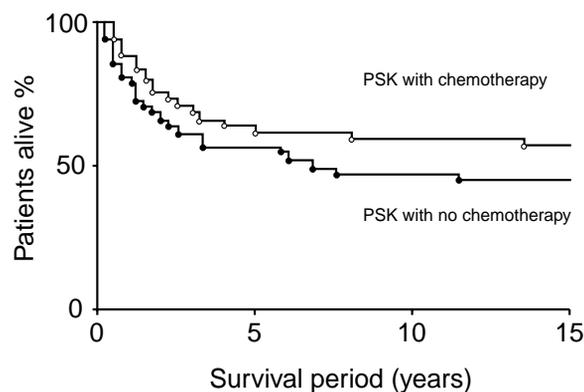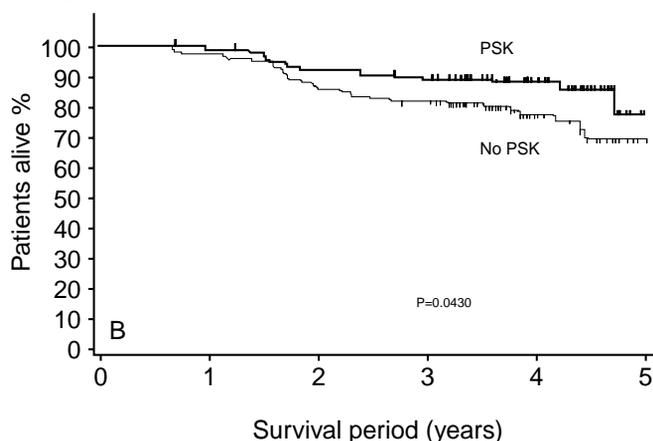
Figure 4a.

Figure 4b.

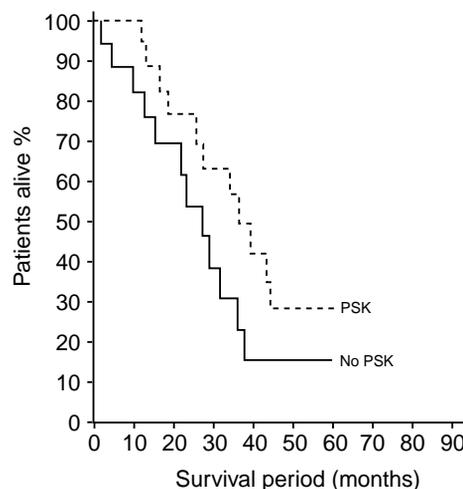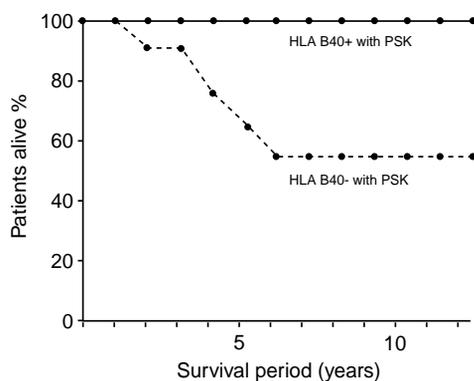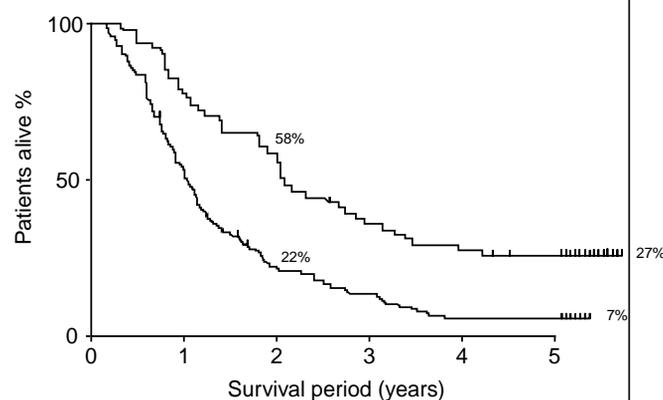**Figure 4c.**

Figure 4d.

Figure 4e.

Figure 4f.

conventional anticancer therapies (radiotherapy and/or chemotherapy), following surgery where appropriate. The PSP dose was 3.1 grams/day, the batyl alcohol 450 mg/day, taken by mouth before meals for two months. Effectiveness was judged by marked improvement of clinical symptoms together with; (a) significant improvement in blood profiles (white cell count, other) and/or immune indices; and/or (b) significant improvement in Karnovsky performance status or body weight. If none of these criteria for effectiveness was met in a patient at the end of the trial period (six months), the treatment was judged ineffective.

Once the code was broken at the end of the trial and the data analyzed, PSP was found effective for 82 percent of the patients versus 45 percent for batyl alcohol (p<0.001). PSP improved clinical symptoms overall. PSP alleviated symptoms commonly associated with cancer, including fatigue, anorexia, nausea, thirst, cold sweat, and pain. PSP also alleviated the severity of systemic toxic deterioration associated with conventional therapies, stabilized or increased body weight, and significantly improved overall immune status. The extent of benefit to patients with specific cancer types is summarized in Table 3.

The success of the Phase II trial justified progression to a well controlled 17-month, multi-center Phase III trial, which was carried out at hospitals in Shanghai, Beijing, and other areas in China, with a total 189 patients. The double-blind study used the same doses and test materials as the previous study, and examined PSP against the same three cancers co-treated with conventional therapies.[59] PSP was effective in 87 percent of patients, versus 42 percent for the shark alcohol (p<0.01), using the same criteria for effectiveness as the Phase II trials.[59] Fatigue, loss of appetite, anorexia, vomiting, dryness of mouth or throat, sweating, and pain all were significantly decreased (p<0.05). PSP lessened fatigue in the greatest

number of patients (81 percent) and pain in the least number (26 percent). PSP also improved most of the other parameters measured in this Phase III trial.[59] Karnovsky performance status significantly improved in 95 percent of the patients (compared to 22% of the controls, p<0.05). White cell count and hemoglobin were significantly improved, as well as interleukin-2, which helps activate killer cells. CD4/T-helper counts were conserved more than in controls, as was the CD4/CD8 ratio. Body weight was maintained and PSP produced no adverse effects.

In the Phase III trial, as well as a number of reports from individual treatment centers, PSP again demonstrated significant benefit against three cancers – stomach, esophagus, and lung.[21,50,63] PSP also ameliorated adverse effects to the bone marrow, liver, skin, and cardiovascular and digestive systems seen in batyl alcohol controls.[50] Sun et al quantified the adverse side-effects attributable to the chemotherapy and radiotherapy regimens, and found markedly lower incidence in the PSP-treated group.[61]

Although the Phase II and III trial designs did not include assessment of long-term survival benefit, in an open-label, randomized trial on esophageal cancer, PSP did significantly improve one-year and three-year survival.[64] In his cogent 1999 review of PSP, Liu noted PSP also has favorable action in patients receiving bone marrow transfusion (BMT) treatment.[65] Taken together, the findings from the Phase II and Phase III trials establish that PSP benefits cancers of the stomach,[62,66-68] esophagus,[62,63,69-71] and lung,[62,72-76] and PSP has been recognized for these applications by China's Ministry of Public Health.

As shown in Table 3, the percentage of patients who experienced benefit from PSP in the Phase II and Phase III trials ranged from 90-97 percent for stomach, 82-87 percent for esophageal, and 70-86 percent for lung cancers, all statistically significant when

Table 3. PSP Controlled Trials Against Various Cancers.

Cancer Type	Authors	Subjects	Outcome
Stomach DOUBLE-BLIND Phase II trial	Liu et al, 1993[62] PSP vs shark oil	78	PSP effective 97% pts. vs. 77% controls (p<0.01). Marked symptomatic improvement
Stomach DOUBLE-BLIND Subgroup Phase II	Zhang et al, 1993[89] PSP vs shark oil	18	PSP increased NK cells (p<0.05)
Stomach DOUBLE-BLIND Subgroup Phase II	Shi, 1993[90] PSP vs shark oil	30	PSP increased NK cells (p<0.01)
Stomach DOUBLE-BLIND Phase III trial	Liu et al, 1999[59] PSP vs shark oil	60	PSP effective 90% pts. vs 40% controls (p<0.01)
Stomach OPEN	Wu et al, 1999[91] PSP vs shark oil	82	PSP increased NK, IL-2, CD4/CD8 ratio (p<0.01)
Esophagus DOUBLE-BLIND Phase II trial	Liu and Zhou, 1993[62] PSP vs shark oil	112	PSP effect. 82% pts. vs. 32% (p<0.001). Marked symptomatic improvement
Esophagus OPEN	Yao, 1999[64] Surg + RT +/-PSP	100	PSP extended 1-yr, 3-yr survival (p≤0.05)
Esophagus DOUBLE-BLIND Phase III trial	Liu et al, 1999[59] PSP vs shark oil	61	PSP effective 87% pts. vs. 43% controls (p<0.01)
Lung DOUBLE-BLIND Phase II trial	Liu and Zhou, 1993[62] PSP vs shark oil	84	PSP effective 70% pts. (>2x controls) (p<0.01). Marked symptomatic improvement
Lung DOUBLE-BLIND Phase III trial	Liu et al, 1999[59] PSP vs shark oil	68	PSP effective 86% pts. vs. 42% controls (p<0.01)
Gynecological (Ovarian, Endometrial)	Sun and Zhu, 1999[60] Chemotherapy +/-PSP	40	PSP improved quality of life (p<0.05)

*Where indicated, conducted within two larger, compounded Phase II and Phase III trials. Herein listed separately for clarity. Statistical data listed as derived by the trial investigators.

compared against figures for controls. Clearly, PSP can benefit the majority of patients afflicted with such cancers, and has the potential to be therapeutic against other cancers as well.[73,77]

Mushroom Immunoceuticals: Mechanisms of Action

The orally-bioactive glucans and proteoglycans isolated from mushrooms are currently the most promising class of immunoceuticals. Without doubt, they are capable of simultaneously augmenting all the key pathways of host immunity. After decades of experimentation with lentinan, PSK, schizophyllan, and PSP, as many potential mechanisms have been identified as the many pathways known to exist in the immune system. Perhaps the single most logical and likely site of action is in dendritic or Langerhans cells (LC).

Dendritic cells, of which Langerhans cells are a skin-residing subset, are capable of sensing foreign or domestically-threatening material and mobilizing an appropriate, timely immune response. PSK injected directly into human stomach tumors prior to surgery was taken up specifically by dendritic cells located in and around the tumors.[78] Tsujitani, Maehara, and their coworkers successfully correlated extended survival of stomach cancer patients with the degree of infiltration of the tumors by LC.[34,79]

Due to their widespread localization throughout tissues, dendritic cells are the first cellular line of defense of the immune system. They are likely to be the first host cells to contact incoming glucan material. As glucans enter the oral cavity, they can be sampled by the LC present in the oral mucosa, and then by dendritic cells in the stomach and intestines. After glucan materials are absorbed and circulate to the liver, the dendritic-like Kupffer cells can sample them. Glucan material reaching lymph nodes can be taken up by dendritic cells residing in the nodes. Carbon-14 radio-labeling of PSK was utilized to prove its large proteoglycan molecules are absorbed and reach the bloodstream intact.[23]

Similar to PSK stimulating dendritic cells, PSP is known to stimulate macrophage or other immune phagocytic activity *in vivo*. When mice were given charcoal intravenously, then fed PSP, both the phagocytic activity of cells in the blood and the clearance of the charcoal from the circulation were significantly accelerated.[80]

These "upstream" activation effects of PSK and PSP on tissue and blood-borne phagocytic cells likely account for their "downstream" effects, which effectively result in heightened anticancer immunity. It is tempting to imagine after being picked up by a dendritic cell or other antigen-sorting cell, PSK and PSP may function as antigenic stimuli. Perhaps their presence above a certain threshold inside a phagocytic immune cell, while innocuous to the cell's survival, in some way activates or primes that cell. Perhaps mushroom glucans and proteoglycans act more crudely, "prodding" the cell to greater antigen-presenting activity.

In killer or pre-killer T-cells, it is possible the close proximity of these immunoceutical substances to the outer cell membrane could result in activation or heightening of activity. Elevated cytotoxic, killer cell activity has been linked *in vivo* to a more positive post-operative clinical course in cancer patients.[81,82] PSK activates killer cells *in vivo*. The instillation of PSK into a human gastric tumor mass prior to resective surgery caused T-cells around the site to become tumor-infiltrating and develop significantly enhanced cytotoxic "killer" activity directed at the tumor. Similar findings were obtained with a 14-day course of PSK in bladder cancer patients.[82] PSK also activates human NK cells in culture at concentrations reached in the blood by normal oral dosing of 3 grams per day.[81,82]

Figure 5. Likely pathways for immune enhancement by mushroom proteoglycans**.**

Modified, from Chihara et al.[8]
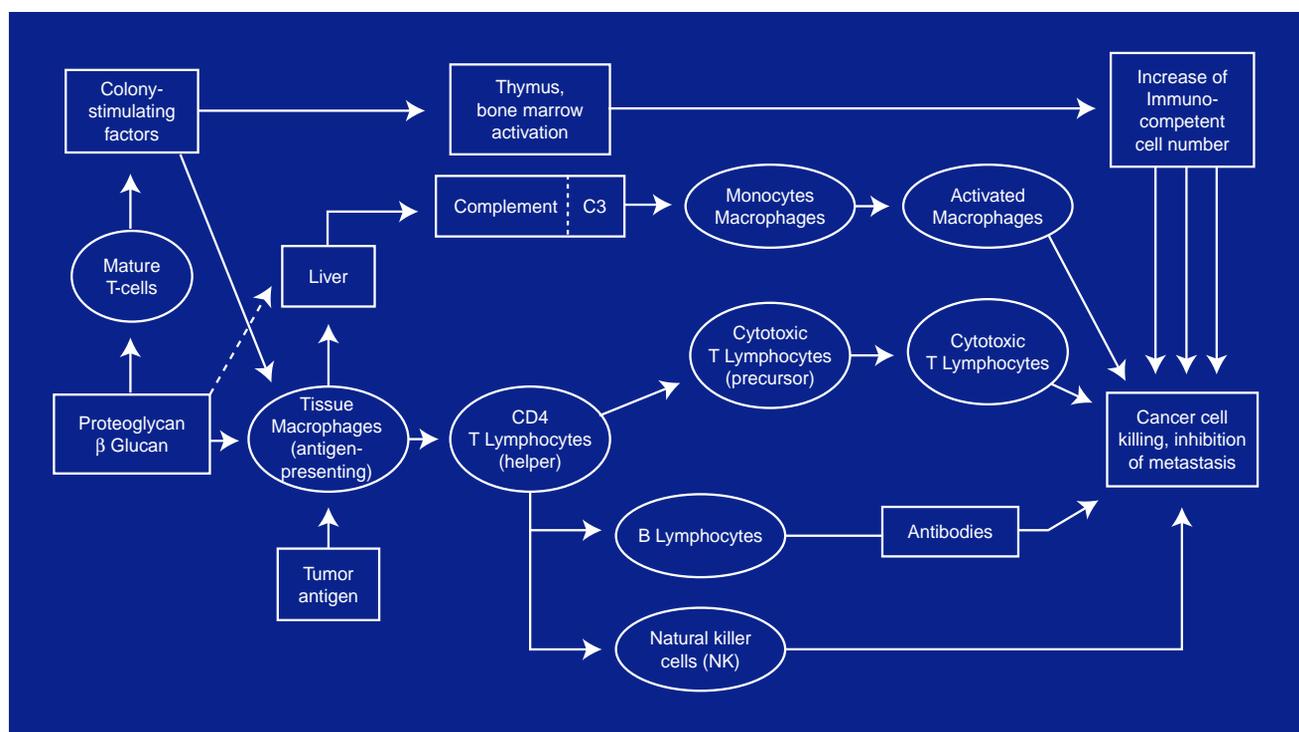
PSP also activates killer cells *in situ* in the living cancer patient. In the Phase II and III double-blind trials, PSP significantly raised NK cytotoxic activity, significantly raised IL-2 levels, and significantly improved the CD4 helper/CD8 suppressor T-cell ratio. Altogether, these are the primary components of anticancer immunity.

Adoptive immunotherapy protocols[81] aim to remove potential killer cells from the patient, activate them with the cytokine IL-2 (interleukin-2), then return them to the body to attack cancerous tissue. But the IL-2 doses required to trigger activation of CD4 and NK cells can have major adverse side-effects. Concomitant dosing of such cells with PSP can cut the required amount of IL-2 by at least half. PSP stimulates lymphokine-activated killer (LAK) cell proliferation by itself at relatively low concentrations and in the absence of IL-2.[83] In mice with suppression of IL-2 production from cyclophosphamide toxicity, PSP supplementation restored IL-2 production to normal.[51]

Another potential avenue of mushroom immunoceutical action is through elevation of immune system cytokines *in vivo*. PSK, PSP, lentinan, and other mushroom immunoceuticals can provoke secretion of cytokines, including IL-1, IL-2, IL-6, IL-8, TNF (tumor necrosis factor) and various interferons from cultured immune cells by as much as 5-120 times baseline levels.[1,2] However, experiments in which antibodies were used to block the actions of individual cytokines clearly demonstrated cytokines were not necessary for PSK to activate human natural killer cells.[81] This finding points to possible cell-to-cell interactions, rather than pharmacologic cytokine activity, as the main focus of mushroom immunoceuticals. The former class of effect would also be more consistent with their pro-homeostatic effects, rather than the adverse effects associated with the use of cytokines in human trials.

A critical assessment of the mechanistic findings from human studies of various mushroom immunoceuticals led to the

composite schematic presented in Figure 5. Many details of mushroom immunoceutical actions are unclear, but their clinical versatility should provide impetus for more precise definition of their modes of action.

Mushroom Immunoceuticals: Valuable Anticancer Tools

A trend toward integration of immunopotentiating agents with the extant cancer regimens of surgery, chemotherapy, and radiation therapy is now considerably advanced in Japan and China – countries where mushroom preparations have been an anticancer resource for centuries. In the West, a more proactive approach to cancer management is long overdue, with the glaring failures of conventional modalities to cure common cancers and the availability of good clinical evidence supporting mushroom immunoceuticals. Misplaced dogma should soon give way to a new round of clinical and basic research aimed at melding this immunotherapy approach into qualitative improvement of cancer survival rates.

The most frequent cause of shortened survival of the patient with cancer is metastasis, occurring with or without invasion of the surrounding tissues by the formed tumors. Surgery often successfully reduces the tumor mass, and chemotherapy or radiation therapy sometimes will further reduce detectable tumors and minimize invasiveness and metastasis. However, these toxic therapies invariably damage host immunity, and small invasive masses or malignant cell clumps (as little as 100,000 cells or less) predictably survive the best efforts to eradicate them. With their capacity to mobilize the immune system against formed tumors as well as metastases, while lessening the adverse side-effects of conventional therapies, mushroom immunoceuticals should offer clinically-attractive options to the thinking oncologist.

Mushroom immunoceuticals compare favorably with classic biological response modifiers, such as BCG, OK-432, LAK cells, or purified cytokines such as interferons, tumor necrosis factor, or interleukin-2. All these are capable of causing fever, chills, rash, edema, arthralgia, hypotension, congestive heart failure, or CNS toxicities.[65] Crude yeast cell wall material, currently being represented as beta-glucan concentrates, reportedly can cause fevers and other problems. The standardized mushroom glucans and polysaccharide-peptide preparations cause no fever, allergy, or other type of intolerance.[2]

With the emergence of putative markers by which their likelihood of efficacy can be monitored – dendritic cell tumor infiltration, killer cell cytotoxic potential *in vitro*, abnormally-low skin DTH, elevated levels of ACT or SA – these safe and effective mushroom immunopotentiators are prime choices for cancer management. In fact, progressive physicians have been using them for years. Certainly the risk-benefit and cost-benefit profiles of mushroom preparations are superior to anticancer pharmaceuticals. Besides being safe to take for periods of years, they improve energy levels in the cancer patient, speed regeneration of damaged bone marrow, support the liver,[84] reduce side-effects of toxic anticancer therapies, and generally raise well-being. PSP also offers analgesic action, which can be beneficial to the cancer patient. Doses up to 15 grams daily have been tolerated long-term without noticeable adverse effects.[59]

Although it has been less thoroughly researched overall than PSK and its long-term benefits to survival are not yet as firmly established, PSP is fast gaining respect as an anticancer therapeutic. Strictly controlled, double-blind trials demonstrated PSP improves quality of life in more than 70 percent of patients with cancer. PSP also lessens the adverse effects of other therapies, while potentiating their curative effects.[50,85] For practitioners hesitant to put full faith in PSP due to its relative lack

of survival data, the use of a combination of PSP with PSK might be worthy of consideration.

The enhanced survival rates achieved by PSK for several cancers are certainly clinically meaningful. Used singly or in combination, PSK and PSP have the potential to extend survival. It may prove instructive, for proponents and skeptics alike, to conduct an integrative cancer trial in which mushroom immunoceuticals play a central role, along with digestive enzymes, thymic extract, vitamin C, coenzyme Q10, omega-3 fatty acids, and other positive-acting immunoceuticals.

Glucan and proteoglycan mushroom immunoceuticals offer hope for cancer patients. These substances are pro-homeostatic, uniquely effective immune boosters, which pose no threat of autoimmune backlash. As dietary supplements, they are safe, clinically proven, and exhibit near-perfect benefit-risk profiles. Mushroom immunoceuticals are a potential boon to individuals afflicted with cancer, living with impaired immunity, or merely descending into ill health with the passing of time.

References

1. Borchers AT, Stern JS, Hackman RM, et al. Mushrooms, tumors, and immunity. *Proc Soc Exp Biol Med* 1999;221:281-293.

2. Wasser SP, Weis AL. Therapeutic effects of substances occurring in higher basidiomycetes mushrooms: a modern perspective. *Crit Rev Immunol* 1999;19:65-96.

3. Sakagami H, Aoki T. Induction of immunopotentiation activity by a protein-bound polysaccharide, PSK (review). *Anticancer Res* 1991;11:993-1000.

4. Yanaki T, Ito W, Tabata K, et al. Correlation between the antitumor activity of a polysaccharide schizophyllan and its triple-helical conformation in dilute aqueous solution. *Biophys Chem* 1983;17:337-342.

5. Bluhm T, Sarko A. The triple helical structure of lentinan, a linear ß-(1-3)-D-glucan. *Can J Chem* 1977;55:293-299.

6. Mizuno T, Saito H, Nishitoba T, et al. Antitumor-active substances from mushrooms. *Food Rev Int* 1995;11:23-61.

7. Alberts B, Watson JD, Bray D, et al. *Molecular Biology of the Cell* (2nd Edition). New York: Garland Publishing; 1989.

8. Chihara G, Hamuro J, Maeda YY, et al. Antitumor and metastasis-inhibitory activities of lentinan as an immunomodulator: an overview. *Cancer Detect Prev Suppl* 1987;1:423-443.

9. Kimura Y, Tojima H, Fukase S, et al. Clinical evaluation of sizofilan as assistant immunotherapy in treatment of head and neck cancer. *Acta Otolaryngol* 1994;511:192-195.

10. Okamura K, Suzuki M, Chihara T, et al. Clinical evaluation of schizophyllan combined with irradiation in patients with cervical cancer. *Cancer* 1986;58:865-872.

11. Okamura K, Suzuki M, Chihara T, et al. Clinical evaluation of schizophyllan combined with irradiation in patients with cervical cancer. A randomized controlled study; a five-year survival rate. *Biotherapy* 1989;1:103-107.

12. Miyazaki K, Mizutani H, Katabuchi H, et al. Activated (HLA-DR+) T-lymphocyte subsets in cervical carcinoma and effects of radiotherapy and immunotherapy with sizofiran on cell-mediated immunity and survival. *Gynecol Oncol* 1995;56:412-420.

13. Nakano T, Oka K, Hanba K, et al. Intratumoral administration of sizofiran activates langerhans cell and T-cell infiltration in cervical cancer. *Clin Immunol Immunopathol* 1996;79:79-86.

14. Various authors. *Active Hexose Correlated Compound*. Purchase, New York: Quality of Life Labs; 1999.

15. Kamiyama Y. Improving effect of active hexose correlated compound (AHCC) on the prognosis of postoperative hepatocellular carcinoma patients. *Eur Surg Res* 1999;31:216.

16. Matsui Y, Kawaguchi Y, Kamiyama Y. Effects of AHCC as a complementary therapy on prognosis of postoperative hepatocellular carcinoma patients. In: *AHCC Research Association 7th Symposium Abstracts*. Purchase, New York: Quality of Life Labs; 1999.

17. Jones K. Maitake: a potent medicinal food. *Altern Comp Ther* 1998;Dec:420-429.

18. Maitake Products Inc. Maitake D-fraction technical support document. Paramus, New Jersey: Maitake Products Inc; 1999.

Mushroom Glucans & Proteoglycans

19. Nanba H. Results of non-controlled clinical study for various cancer patients using maitake D-fraction. *Explore* 1995;6:19-21.

20. Maitake Products Inc. Maitake D-fraction obtained IND for clinical study (press release). Paramus, New Jersey: Maitake Products Inc; 1998.

21. Jong S, Yang X. PSP – a powerful biological response modifier from the mushroom Coriolus versicolor. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:16-28.

22. Yang QY, Kwok CY, Xu SJ, eds. *1993 PSP International Symposium Anthology of Theses and Abstracts*. Shanghai: Fudan University Press; 1993.

23. Ikuzawa M, Matsunaga K, Nishiyama S, et al. Fate and distribution of an antitumor protein-bound polysaccharide PSK (Krestin). *Intl J Immunopharmacol* 1988;10:415-423.

24. Kaibara N, Soejima K, Nakamura T, et al. Postoperative long-term chemotherapy for advanced gastric cancer. *Jpn J Surg* 1976;6:54-59.

25. Fujimoto S, Takahashi M, Minami T, et al. Clinical value of immunochemotherapy with OK-432. *Jpn J Surg* 1979;3:190-196.

26. Hattori T, Niimoto M, Koh T, et al. Post-operative long-term adjuvant immunochemotherapy with mitomycin-C, PSK and FT-207 in gastric cancer patients. *Jpn J Surg* 1979;9:110-117.

27. Kodama Y, Kano T, Tamada R, et al. Combined effect of prophylactic lymphadenectomy and long-term combination chemotherapy for curatively resected carcinoma of the stomach. *Jpn J Surg* 1982;12:244-248.

28. Kondo M, Torisu M. Evaluation of an anticancer activity of a protein-bound polysaccharide PS-K (Krestin). In: Torisu M, Yoshida T, eds. *Basic Mechanisms and Clinical Treatment of Tumor Metastasis*. New York: Academic Press; 1985:623-636.

29. Mitomi T, Ogoshi K. Clinical study of PSK as an adjuvant immunochemotherapeutic agent against gastric cancer. *Jpn J Cancer Chemother* 1986;13:2532-2537.

30. Niimoto M, Hattori T, Tamada R, et al. Postoperative adjuvant immunochemotherapy with mitomycin C, futraful and PSK for gastric cancer. An analysis of data on 579 patients followed for five years. *Jpn J Surg* 1988;18:681-686.

31. Maehara Y, Moriguchi S, Sakaguchi Y, et al. Adjuvant chemotherapy enhances long-term survival of patients with advanced gastric cancer following curative resection. *J Surg Oncol* 1990;45:169-172.

32. Nakazato H, Koike A, Saji S, et al. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. *Lancet* 1994;343:1122-1126.

33. Hattori T, Nakajima T, Nakazato H, et al. Postoperative adjuvant immunochemotherapy with mitomycin C, tegafur, PSK and/or OK-432 for gastric cancer, with special reference to the change in stimulation. *Jpn J Surg* 1990;20:127-136.

34. Tsujitani S, Kakeji Y, Orita H, et al. Postoperative adjuvant immunochemotherapy and infiltration of dendritic cells for patients with advanced gastric cancer. *Anticancer Res* 1992;12:645-648.

35. Kondo M. Immunotherapy as adjuvant treatment after curative resection of gastric cancer. *Lancet* 1994;344:274.

36. Torisu M, Hayashi Y, Ishimitsu T, et al. Significant prolongation of disease-free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. *Cancer Immunol Immunother* 1990;31:261-268.

37. Mitomi T, Tsuchiya S, Iijima N, et al. Randomized, controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. *Dis Colon Rectum* 1992;35:123-130.

38. Okudaira Y, Sugimachi K, Inokuchi K, et al. Postoperative long-term immunochemotherapy for esophageal carcinoma. *Jpn J Surg* 1982;12:249-256.

39. Ogoshi K, Satou H, Isono K, et al. Possible predictive markers of immunotherapy in esophageal cancer: retrospective analysis of a randomized study. *Cancer Invest* 1995;13:363-369.

40. Ogoshi K, Kondoh Y, Tajima T, et al. Glycosidically bound sialic acid levels as a predictive marker of postoperative adjuvant therapy in gastric cancer. *Cancer Immunol Immunother* 1992;35:175-180.

41. Go P, Chung CH. Adjuvant PSK immunotherapy in patients with carcinoma of the nasopharynx. *J Int Med Res* 1989;17:141-149.

42. Hayakawa K, Mitsuhashi N, Saito Y, et al. Effect of Krestin (PSK) as adjuvant treatment on the prognosis after radical radiotherapy in patients with non-small cell lung cancer. *Anticancer Res* 1993;13:1815-1820.

43. Sugimachi K, Inokuchi K, Matsuura H, et al. Hormone conditioned cancer chemotherapy for recurrent breast cancer prolongs survival. *Jpn J Surg* 1984;14:217-221.

44. Toi M, Hattori T, Akagi M, et al. Randomized adjuvant trial to evaluate the addition of tamoxifen and PSK to chemotherapy in patients with primary breast cancer. *Cancer* 1992;70:2475-2483.

45. Morimoto T, Ogawa M, Orita K, et al. Postoperative adjuvant randomised trial comparing chemo-endocrine therapy, chemo-therapy and immunotherapy for patients with stage II breast cancer: 5-year results from the Nishinihon cooperative study group of adjuvant chemo-endocrine therapy for breast cancer (ACETBC) of Japan. *Eur J Cancer* 1996;32A:235-242.

46. Iino Y, Yokoe T, Maemura M, et al. Immunochemotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer. *Anticancer Res* 1995;15:2907-2912.

47. Yokoe T, Iino Y, Takei H, et al. HLA antigen as predictive index for the outcome of breast cancer patients with adjuvant immunochemotherapy with PSK. *Anticancer Res* 1997;17:2815-2818.

48. Ohno R, Yamada K, Masaoka T, et al. A randomized trial of chemoimmunotherapy of acute nonlymphocytic leukemia in adults using a protein-bound polysaccharide preparation. *Cancer Immunol Immunother* 1984;18:149-154.

49. Kawa K, Konishi S, Tsujino G, et al. Effects of biological response modifiers on childhood ALL being in remission after chemotherapy. *Biomed Pharmacother* 1991;45:113-116.

50. Yang QY. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999.

51. Yang Q. Yun Zhi polysaccharopeptide (PSP) and the general aspects of its research. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:29-38.

52. Yang Q. History, present status and perspectives of the study of Yun Zhi polysaccharopeptide. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:5-15.

53. Jiang X, Huang L, Zhou Y, et al. Subchronic toxicity test of polysaccharopeptide of Yun Zhi (PSP). In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:272-284.

54. Zhong B, Zhou Y, Zhou L, et al. Genetic toxicity test of Yun Zhi polysaccharopeptide (PSP). In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:285-294.

55. Qian Z, Zhou L, Zhang Z, et al. The test of PSP on the cause of the abnormal fetus in two generations of rats. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:158-177.

56. Xu G. Phase I clinical test report of PSP capsules. In: Yang, Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:179-182.

57. Sun Z, Lu M, Feng J. The preliminary appraisal of poly-saccharide-peptide (PSP) in malignant and non-malignant diseases. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:257-258.

58. Gao Y. The evaluation of PSP capsules in clinical pharmacology. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:209-215.

59. Liu J, Zhou J, Liu T. Phase III clinical trial for Yun Zhi polysaccharopeptide (PSP) capsules. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:295-303.

60. Sun T, Zhu Y. The effect of PSP on immune function and living quality in patients receiving chemotherapy for gynecological malignancies. In: Yang Q, ed. *Advanced Research in PSP*, 1999. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:308-309.

61. Sun Z, Yang Q, Fei H. The ameliorative effect of PSP on the toxic and side reactions of chemo-and radiotherapy of cancers. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:304-307.

Mushroom Glucans & Proteoglycans

62.   Liu J, Zhou J. Phase II clinical trial for PSP capsules. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:183-208.

63.   Yang Q, Zhou Y. A protein bound polysaccharide-PSP. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:22-31.

64.   Yao W. Prospective randomized trial of radiotherapy plus PSP in the treatment of esophageal carcinoma. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:310-313.

65.   Liu T. PSP in clinical cancer therapy – a review. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:68-75.

66.   Shi J, Chen T, Zhao Y. Protective effects of PSP for the patients with gastric cancer during chemotherapy. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:329.

67.   Xie S. The effect of PSP on red-cell immunity – a clinical study on gastric cancer patients. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:241-242.

68.   Xu G. The effects of PSP on improving immunity for gastric cancer patients (abstract). In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:263-264.

69.   Liu T. Role of PSP in the radiation treatment of esophagus cancer. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:224-231.

70.   Wu Z, Chen C, Chen Y. Clinical observation of esophageal treatment by radiotherapy together with the oral administration of PSP. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:265-268.

71.   Wu Z, Wang Z. Clinical curative effects observation on NSCLC and esophageal cancer by radiotherapy and chemotherapy combined with PSP. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:326.

72.   Ke L. Observation on the substance selected as an accessory treatment for lung cancer. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:273.

73.   Liao M, Zhao J. The II stage clinical tests of PSP in the treatment of lung cancer. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:243-256.

74.   Wang G. Clinical observations of Yun Zhi polysaccharopeptide (PSP) capsule for the supplementary treatment of esophageal, gastric and lung cancer due to radio-chemo-therapy. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:333-334.

75.   Ke L, Yao P, Gao Z, et al. An observation on the effects of polysaccharide peptide (PSP) as an accessary treatment for lung cancer. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:331.

76.   Zhong W. Clinical research using PSP and chemotherapy for lung cancer. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:332.

77.   Chen Z, Yang M, Zhu P. Research and application of the anticancerous mechanism of the purified PSP (PCV). In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:151-152.

78.   Tomochika H, Gouchi A, Okanobu K, et al. The effect and distribution of a protein-bound polysaccharide preparation, PSK (Krestin), intratumorally injected prior to surgery into gastric cancer patients. *Acta Med Okayama* 1989;43:289-297.

79.   Tsujitani S, Furukawa T, Tamada R, et al. Langerhans cells and prognosis in patients with gastric carcinoma. *Cancer* 1987;59:501-505.

80.   Yang Q, Hu Y, Li X, et al. A new biological response modifier substance – PSP. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:56-72.

81.   Kariya Y, Inoue N, Kihara T, et al. Activation of human natural killer cells by the protein-bound polysaccharide PSK independently of interferon and interleukin 2. *Immunol Lett* 1992;31:241-246.

82. Mizutani Y, Yoshida O. Activation by the protein-bound polysaccharide PSK (Krestin) of cytotoxic lymphocytes that act on fresh autologous tumor cells and T24 human urinary bladder transitional carcinoma cell line in patients with urinary bladder cancer. *J Urol* 1991;145:1082-1087.

83. Jian Z, Zhang W, Li S. The effect of PSP on LAK cell functions. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:143-150.

84. Yeung JH, Chiu LCM. Effect of polysaccharide peptide (PSP) on glutathione and protection against paracetamol-induced hepatotoxicity in the rat. *Methods Find Exp Clin Pharmacol* 1994;16:723-729.

85. Yao P, Gao Z, Fang S, et al. Evaluation of the subsidiary effects of taking PSP orally on the chemotherapy of stomach cancer. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:269-270.

86. Shen Q, Shu H, Shen D. PSP will bring hope and life to cancer patients. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:274-282.

87. Aoki T, Usuda Y, Miyakoshi H, et al. Low natural killer syndrome: clinical and immunologic features. *Nat Immun Cell Growth Regul* 1987;6:116-128.

88. Kikuchi Y, Kizawa I, Oomori K, et al. Effects of PSK on Interleukin-2 production by peripheral lymphocytes of patients with advanced ovarian carcinoma during chemotherapy. *Jpn J Cancer Res* 1988;79:125-130.

89. Zhang L. II Stage clinical test report of PSP capsules in the Shu Guang Hospital. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:269-262.

90. Shi J. PSP for the protection of the tumorous patients during chemotherapy. In: Yang Q, Kwok C, eds. *PSP International Symposium 1993*. Hong Kong: Fudan University Press; 1993:271-272.

91. Wu C, Wu J, Sun W. The curative effect of Yun Zhi polysaccharopeptide (PSP) on stomach cancer. In: Yang Q, ed. *Advanced Research in PSP, 1999*. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:322-323.

Mushroom Glucans & Proteoglycans