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Medicinal Value of Turkey Tail Fungus *Trametes versicolor* (L.:Fr.) Pilát (Aphyllophoromycetideae). A Literature Review*

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ABSTRACT: *Trametes* (=*Coriolus*) *versicolor* (L.:Fr.) Pilát, is a small, flexible polypore fungus that is an important part of the forest ecology as a recycler of dead and dying trees in forests throughout the world. Of all the mushrooms used today for their medicinal qualities, more research has been performed on this species than any other, including shiitake (*Lentinus edodes*), or reishi (*Ganoderma lucidum*). High-molecular-weight fractions from the mycelium have been studied in human clinical trials, especially polysaccharide Krestin (PSK), which is an approved drug paid for by national health care in Japan. PSK is given orally (often 3 grams/day), along with several chemotherapy protocols. Numerous *in vitro* and *in vivo* studies show enhancement of immune functions, antiviral effects, and cholesterol-regulating effects, among others. New clinical trials demonstrate improved quality of life after surgery and in combination with chemotherapy, as well as extended 5- and 10-year survival rates, especially for patients with colorectal and stomach cancers. Further studies are needed in order to clarify the most effective forms of the whole fruiting body extracts, mycelium extracts, and their high-molecular weight fractions, along with the optimum dose. Safety issues, while not completely determined for long-term treatment, during pregnancy, or in combination with pharmaceutical drugs, seem to be of low concern, with no noted published side effects or interactions with drugs reported.

KEY WORDS: *Trametes versicolor*, turkey tail fungus, polysaccharide Krestin, traditional Chinese medicine, medicinal mushrooms, immunosuppressive acidic protein

ABBREVIATIONS

CT: chemotherapy; **CQ:** carbazilquinone; **DC:** dendritic cells; **5′-DFUR:** doxifluridine; **ECG:** electrocardiogram; **FT:** FT-207, a furanyl analog of 5-fluorouracil; **5-FU:** 5-fluorouracil; **HLA:** human leukocyte-associated antigens; **HSPx:** heat shock protein; **i.p.:** intraperitoneal; **IL-x:** interleukin; **IAP:** immunosuppressive acidic protein; **IFN:** interferon; **iNOS:** Inducible nitric oxide synthase; **i.v.:** ntravenale; **LPO:** lipoperoxide; **M-CSF:** macrophage colony-stimulating factor; **MMC:** mitomycin-C; **MMP-x:** matrix metalloproteinase; **MOLT-4:** human lymphoblastic leukemia cell; **MT-4:** membrane type-4; **NO:** nitric oxide; **NSCLC:** non-small cell lung cancer; **OK:** OK-432, chemotherapeutic agent; **PG:** prostaglandin; **PKC:** protein kinase C; **PLCC:** postoperative long-term cancer chemotherapy; **p.o.:** oral method; **PPD:** purified protein derivative; **PMN:** polymorphonuceocytes; **PSK:** polysaccharide krestin; **PSP:** polysaccharopeptide; **RT:** radiotherapy; **SOD:** superoxidedismutase; **SPCV:** small polypeptide *Trametes versicolor;* **STAT:** signal transducer and activator of transcription; **TCM:** traditional Chinese medicine; **TGF-x:** transforming growth factor; **Th1/Th2:** T-helper cels; **TNF:** tumor-necrosis factor; **Tv:** *Trametes versicolor;* **WBC:** white blood cells.

* An updated version of this monograph with additional material will be published in a forthcoming book by Christopher Hobbs, *Medicinal Mushrooms,* Third Edition, New York: Thieme Medical Publishers, Inc., ISBN: 1-58890-298-6. To reserve a copy upon publication, call 800-782-3488, fax +1-212-947-1112, or visit www.thieme.com.

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INTRODUCTION

Trametes (=Coriolus) versicolor (L.:Fr.) Pilát (turkey tail; in Japan, *T. versicolor* is known as *kawaratake,* which means "mushroom by the river bank"; in China, the fungus is called yun-zhi (Yang et al., 1993), meaning "cloud fungus." It has been renowned in Japan and China as medicine for thousands of years. *T. versicolor* one of the most easily identifiable polypores and the most common wood rotting species on dead hardwoods; this multicolored mushroom is recognized throughout the world and is thought to have had a long history of use. Native to tropical, subtropical, and temporate zones, this species is highly adaptive, growing on the widest assortment of woods. Turkey tail is one of the most potent and the best studied of all medicinal mushrooms (Hobbs, 1995; Stamets, 2000). High-molecular-weight fractions from the mycelium have been studied in human clinical trials, especially PSK (polysaccharide Krestin), which is an approved drug paid for by national health care in Japan.

HISTORY

A patient with stomach cancer reported benefits from an herbal tea called *Saru-no-koshikake,* which contained turkey tails as an ingredient (Mitomi et al., 1992).

PSK, the first polysaccharide fraction from turkey tails, was first approved by the Japanese Ministry for the treatment of cancer in 1977, and by 1987 it accounted for 25.2% of the total national expenditure for anticancer agents (Fukushima, 1989; Mizuno, 1999). Florists in Europe recently adopted this fungus as one of the top species for commercial design (Poppe and Heungens, 1991).

CHEMISTRY

The lipid fraction from the carpophores of *T. versicolor* amounts to 1.7% of the total weight and contains the lanostane-type tetracyclic triterpenoid ergosta-5,7,22,trien-3-ol (ergosterol) as the major sterol (common in many other Polyporaceae), along with smaller amounts of ergost-7-en-3-ol (fungisterol) (Yokoyama et al., 1975; Endo, 1981). They also contain β-sitosterol, stigmast-5-en-3-ol (Kim et al., 1979), and hydroxymethylquinoline (Abraham and Spasov, 1991). A sesquiterpene, coriolin, and deoxycoriolic acid have been isolated from the related species, *T. consors* (Zhou and Yang, 1999).

The predominance of chemical, pharmacological, and toxicological data is on two principal immunologically active polysaccharide-protein complexes with approximate molecular weights of 100 kDa from *T. versicolor*, PSP (polysaccharopeptide), and PSK (polysaccharide "Krestin"). Both complexes are produced commercially by deep-layer cultivation of the mycelium COV-1 and CM-101 strains. PSK is composed of a complex of strand of β-glucans (glucose polymers) bound to polypeptide chains containing high amounts of aspartic and glutamic acids, along with lower amounts of many other amino acids (Tsukagoshi et al., 1984; Fungi Research Institute, 1993). The carbohydrate glucan backbones have main chains with β1→3 linkages and varying degrees of branching at 4′ and 6′. These bond to polypeptides through *O*- or *N*-glycosidic links. PSK powder is soluble in water, is practically insoluble in ethanol, and contains 34–35% carbohydrate (ca. 92% glucan) and 28–35% protein (Ueno et al., 1980). Zhang et al. (2001) determined the approximate monosaccharide content to be D-glucose 1, D-mannose 0.074, D-galactose 0.067, and xylose 0.0178.

These compounds are variously called in the literature *glycoproteins, proteoglycans,* or *polysaccharopeptides.* They may be most related to the glycoproteins (Nelson and Cox, 2000). These are not yet fully characterized and may be related to the integrins and other signaling molecules of plant and animal cells. These are information rich and have many opportunities for hydrogen bonding and other electrostatic interactions.

PSP, first isolated in 1983, is similar in composition to PSK, and includes small amounts of 1→3, 1→4, and 1→6 linked galactose molecules, also 1→6 mannose and 1→4 arabinose linkages (Yang and Zhou, 1993). The similarities and differences between PSP and PSK have been detailed by the Fungi Research Institute (1993). Both PSP and PSK

have been found to be immunomodulating and effective against tumor cells.

The high-molecular-weight glucans from PSP, and PSK associated with the cell walls of many species of fungi vary considerably in their degree of branching, molecular weight, and amounts of other sugars and amino acid residues. Some are α-glucans, and some are true heteropolysaccharides (Ooi and Liu, 2000).

The glucans are also associated with other sugar polymers such as mannose. For instance, when the monosaccharides from *Trametes versicolor* were analyzed after being hydrolyzed, they found a proportional composition of glucose 1.0, mannose 0.074, galactose 0.067, and xylose 0.0178 (Zhang et al., 2001). Tertiary structures may also play a role in the immunomodulating effects of various glucans. One group showed the triple-helix configuration of some native glucans is important for activity (Falch et al., 2000), while other groups have found similar activity in all the β-glucans they tested, higher activity in larger molecular weight glucans and in glucans with increased β-1→6 crosslinking, at least in yeast glucans (Sakagami et al., 1989; Okazaki et al., 1995; Kulicke et al., 1997; Cleary et al., 1999).

The importance of intact tertiary structures, especially in finished products, may be notable, because solvents and heat during the processing of various species may change or completely disrupt them. What effect this has on activity is not clear, and it is not known what configurations of these different compounds lead to the highest immunomodulatory responses, let alone the greatest clinical efficacy, in humans. Traditional preparations of medicinal species, used for thousands of years, might give some support to the idea that a hot-water extraction (decoction) might preserve at least part of the activity. Commercial preparations today are made from hot water extracts, which are said to remove the thermostable polysaccharopeptides, which are then concentrated and purified (Cui and Chisti, 2003).

The amount of purification of a crude extract of *Trametes versicolor* (Tv) will affect its effectiveness as an immunomodulator and antitumor substance. In one study, immunosuppressive acidic protein (IAP) was induced in the serum of mice treated with PSK and other crude extracts of Tv, but not in the serum of mice treated with purified β-glucan from Tv (Ebina, 2001).

Miyazaki et al. (1974) isolated an antitumor polysaccharide that did not contain nitrogen and called it *coriolan.* Several patents were taken out on coriolan, but no further research has been published in the international literature since 1986 (Sumio et al., 1986).

BIOLOGICAL EFFECTS

Many preliminary *in vivo* and *in vitro* studies have shown that PSK has wide immunomodulatory effects and a broad antineoplastic scope when administered orally or by injection. At least one group demonstrated probable absorption of ^{14}C-labeled PSK from the digestive tract into the blood and subsequent migration to bone marrow, salivary glands, brain, liver, spleen, pancreas, and tumor tissue (Ikuzawa et al., 1988). They report that about 70% was excreted in the expiratory air after 24 hours and 15–20% in the urine after 72 hours. PSK had different fates after absorption in mice, based on a PSK antibody-indirect immunofluorescent staining model (Endoh et al., 1988).

Although by far the greatest amount of research has been performed on PSP and PSK, whole mushroom extracts are widely produced for use as dietary supplements and professional products for clinical use by a wide range of practitioners. The aqueous extract of Tv is reported to contain PSP-like molecules of various molecular weights. The larger molecules are said to have the highest immunomodulatory effects. Hydroalcoholic extracts are likely to have less activity, partly because the high-molecular weight compounds are precipitated by alcohol and may not go into solution.

Immunomodulating Effects

Studies show PSP, PSK, and whole fruiting body and mycelial extracts have a broad spectrum of immunological effects, some of which might be triggered by contact with immune tissue in the digestive tract. Mushroom cell wall components

such as PSP are likely to interact with Langerham cells in the mouth and have complex interactions with dendritic cells in the Peyer's patches in the small intestine (Tomochika et al., 1989). Through these interactions, many kinds of immune cells are subsequently affected. Tv extracts, *in vitro* and *in vivo*, given p.o. or i.p. are known to stimulate activity and proliferation of T cells, B lymphocytes, monocytes and macrophages, bone marrow cells, natural killer cells, and lymphocyte-activated killer cells. Increased secretion of antibodies, increased phagocytic functions of the reticuloendothial system, and an inducer of the gene expression of cytokines (IL-2, IL-6, interferons, and TNF) was also seen (Tsukagoshi et al., 1984; Li et al., 1990; Chu et al., 2002). These effects were associated with stimulation of ex vivo tumor cytotoxic activity of splenocytes and T-killer cells in mice. Tv extracts often have a greater immunological effect in animals with depressed immunological function associated with tumor implantation or chemotherapy than in those with normal immune function. However, more effective therapeutic results are seen in animals and in human trials when some intact immune function is present (Nomoto et al., 1983).

Researchers (Wu et al., 1998) report that a protein-bound polysaccharide (PSP) derived from the mycelium of *Trametes versicolor* has different immunological effects in normal mice, depending on their age. In young mice (5 months old), PSP in the diet produced no obvious immuno-enhancing effects at dietary concentrations of up to 1%. However, in old mice (23 months), PSP as 1% of the diet produced a significant, though modest immuno-enhancing effect (Wu et al., 1998).

For a review of the early pharmacological work performed on PSP, see Yang et al. (1992).

Immunological Effects of Aqueous Tv Extracts

Cell-Mediated Immunity

Activation and increased proliferation of immune cells

- Promoted lymphocyte proliferation at concentrations of 100–800 µg/mL *in vitro* (Li et al., 1990). Both lymphocytes and macrophages were activated *in vitro* after exposure to PSP, but no direct cytotoxicity was noted against fibroblasts, hepatoma, or choriocarcinoma cells (Wang et al., 1986).

Reticuloendothelial System Activation

- Phagocytic functions were enhanced (Mayer, 1980; Li et al., 1990).
- PSK administered to mice without induced immunodeficiency stimulated increased production of NO in PMNs, along with IFN-γ, but the increase was not enough to induce tumor cell killing *in vitro* (Asai et al., 2000).

Cytokine Modulation

- In a study involving 27 patients with digestive cancers and nine healthy volunteers, PSK (3 g/day) was reported to counteract the M2-dominant condition, perhaps through improvement of the Th1/Th2 ratio. A number of studies have shown that an imbalance in Th1 and Th2 responses can relate directly to cell-mediated impairment in patients with advanced cancers (Hazama and Oka, 2002).
- In colon-tumor-bearing mice, IFN-γ production was increased nonstatistically and IL-4 significantly decreased when PSK was administered p.o. IL-12 was increased when spleen cells were stimulated with Con A with PSK *in vitro*. These results suggest the ability of PSK to shift the Th1/Th2 balance toward Th1 dominance in tumor-bearing mice (Wada et al., 2003).
- IL-2 production and the delayed-type hypersensitivity response from activated T-lymphocytes was restored after suppression by cyclophosphamide. Interferon-α and -γ induction by human peripheral leukocytes at 10–1000 µg/mL was seen (Li et al., 1990).
- Interferon and the gene expression of interleukin (IL)-12 was increased in the spleen of tumor-bearing mice inoculated with *Candida albicans* after an oral dose of PSK (Ohmura et al., 2003). PSP enhanced IFN-α and IFN-γ in human peripheral leukocytes 4 and 8 times higher, respectively, than in control groups (Li et al., 1990).

Dendritic Cell Viability

- PSK reversed inhibition of functional maturation of dendritic cells (DC) exposed to tumor-derived factors *in vitro*. DC are important antigen-presenting cells promoting tumor-inhibiting immune effects in animals (Okuzawa et al., 2002).

- PSK could counteract dendritic cell cytokine-mediated immunosuppresion in patients with advanced cancers when given in combination with radiation or chemotherapy (Kanazawa et al., 2003).

T-cell Maturation

- Reduction in CD4-positive T cells seen in tumor-bearing mice was prevented by PSK (Ohmura et al., 2003).

Natural Killer Cell Activity, Viability

- PSK decreased expression of protein kinase C-α and increased PKC-δ and PKC-ε levels, showing that PSK and IL-2 stimulate NK cells through different effects on PKC isoenzymes (Garcia-Lora et al., 2003).
- PSP reversed the suppression of natural killer cell function, as well as lymphocyte proliferation and white blood cell production caused by cyclophosphamide (Qian et al., 1997). PSP given orally (1.2 g/day) did not offer protective effects against cyclophosphamide-induced cytopenia in rats. PSP at 1.2 g/day did not change neutrophil, lymphocyte, or platelet counts in rats given i.v. cyclophosphamide (60 mg/kg) (Zhou et al., 1996).

Humoral Immunity

Antibody production

- PSK (oral) restored antibody (IgG) production in mice bearing Sarcoma 180, but not in normal mice (Hobbs, 1995).

Protective Effects

- Prolongs survival time of irradiated mice (Zhu, 1987).
- Reversed the atrophy of the gut-associated lymphoid tissue (GALT) in rats and increased the number of Peyer's patches and the number of thoracic duct lymphocytes induced by total parenteral nutrition, a condition that is known to happen in humans (Nakasaki et al., 1997).
- After lethal infection of mice by *Candida albicans*, i.p. administration of PSK doubled survival time. The most effective dose was 250 mg/kg 24 hours before infection. PSK induced gene expression of TNF-α and increased leukocyte function after 6 hours to 1 day after inoculation. β-1-3-glucanase significantly reduced the effectiveness of PSK (Ohmura et al., 2001).
- Increased granulocyte production in cyclophosphamide-induced granulocytopenia in mice i.p. (Mayer and Drews, 1980).
- PSK had a suppressive effect on the expression of heat shock protein HSP47 and HSP60 but not HSP72/73 at the mRNA level in human tumor strains. HSPs have recently been suggested as an autoantigen in autoimmune diseases (Morino et al., 1997).
- An extracellular polysaccharide from *Trametes versicolor* administered to mice (i.p. or p.o.) challenged with herpes or influenza viruses caused serum interferon induction and inhibited a decrease in phagocytosis (Chen, 1986).

Effects of PSK on Prostaglandin Metabolism

PSK stimulated PG-12 production from rat endothelial cells, suppressing platelet aggregation (Takahata et al., 1985).

Antitumor, Anticancer Effects

In many parts of the world, Tv extracts are used as adjuvants in cancer therapy, both as prescription items, for instance in Japan, or as dietary supplements taken by patients along with conventional treatment, with or without the knowledge of their physicians. As health food supplements they are also increasingly consumed with the idea that they might help prevent or assist the body with cancer, aging, viral infections (such as the common cold), and a host of other ailments.

As a cancer-preventive agent used on a regular basis as a supplement, Tv extracts can possibly inhibit carcinogenesis by reducing the effects of some carcinogens, such as those occuring in tobacco smoke or asbestos, on susceptible host cells.

The use of Tv extracts during conventional cancer treatments, such as chemo- and radiation therapy, have a rational basis because some research shows that it might reduce the possibility of secondary malignancies induced by radiotherapy and cytotoxic chemotherapy. Tv extracts can also protect healthy host cells during radiation and chemotherapy treat-

ments by either directly or indirectly acting as an antioxidant, reducing the effects of oxidative stress. The immunoprotective effects of Tv extracts might be particularly useful for immunocompromised patients such as the elderly or patients with HIV or other infections who choose to undergo chemo- or radiation therapy.

In vitro and *in vivo* studies show that *Trametes versicolor* demonstrates anticancer, antitumor, anticarcinogenenic, and antiproliferative effects. These effects can be at least partly explained by a number of specific biological effects, such as inhibition of metalloproteinases and other enzymes related to metastatic activity and their ability to suppress cancer cell growth and increase the expression of tumor cell surface antigens such as human leukocyte-associated antigens (HLA), which can enhance recognition and thus elimination of the cancer cell by the host immune system (Iguchi et al., 2001).

The impaired antitumor $CD4^+$ T-cell response in gut-associated lyphoid tissue (GALT) of pathogen-free mice was improved by an oral dose of PSK, which suppressed the growth of colon 26 carcinoma inoculated into the cecum, augmented the tumor-neutralizing activity of mesenteric lymph node cells, and decreased the levels of immunosuppressive factors such as transforming growth factor (TGF)-β (Harada et al., 1997).

A 70% ethanolic extract of the fruit bodies reduced cell growth of hormone-responsive human prostate cancer cells and downregulated the production of PSA. It had less effect on androgen-unresponsive prostate cancer cells. The extract increased levels of the signal transducer and activators STAT 1 and STAT 3 in one of these cell lines (Hsieh and Wu, 2001).

Antitumor, Anticancer Effects of Tv Extracts

Inhibition of Tumor Cells

Inhibition of DNA Synthesis

- PSK dose-dependently inhibited DNA synthesis in MCF-7, a human breast cancer cell line. A PSK dose of 200 μg/ml caused a 50% inhibition of DNA synthesis (Aoyagi et al., 1997).
- DNA synthesis in human breast cell cancer line MCF-7 was reduced *in vitro* (50% inhibition at 200 μg/ml) and estrogen receptor (ER) expression on MCF-7 cells was not changed by exposure to PSK. At high PSK concentrations, ER expression decreased (Aoyagi et al., 1997).

Enhancement of Cytokine Production

- PSP activated human natural killer cells to increased cytotoxicity against several different tumor cells lines, which resembled the effects of IL-2 in the same systems. The highest activity was seen at 100 μg/ml. The activation was inhibited when the concentration was 1000 μg/ml (Pedrinaci et al., 1999).
- PSK induced up-regulation of interferon-gamma (IFN-gamma)-expression and down-regulation of transforming growth factor-beta (TGF-beta)-expression, and augmented the manganese superoxide dismutase (Mn-SOD) in tumor tissue from an implanted cancer cell clone line (QR-32) in mice (Habelhah, 1998). Down regulation of TGF-beta and other invasion-related factors such as uPA, MMP-2, and MMP-9 could suppress tumor cell invasiveness (Zhang et al., 2000).
- PSP injected into nude mice alone along with C6 rat glioma cells did not reduce tumor volumes, nor did it enhance the tumor-suppressive effects of radiation, but it did increase NK cell, lymphocyte, and granulocyte counts in blood and spleen, counteracting some of the immunosuppresive effects of radiation treatment (Mao et al., 2001).
- PSP has been observed to enhance the transcription of tumor necrosis factor gene in mouse peritoneal macrophages, indicating an immunomodulatory effect of PSP (Liu et al., 1993).

Antitumor Effect

- PSK has shown antitumor activity in animals with adenosarcoma, fibrosarcoma, mastocytoma, plasmacytoma, melanoma, sarcoma, carcinoma, and mammary, colon, and lung cancer (Tsukagoshi et al., 1984).
- PSP showed tumor-inhibiting activity in animals with Sarcoma 180, P388 leukemia, monocytic leukemia, Ehrlich ascitic tumor, histiocytic lymphoma, human lung adenocarcinoma, and various cancers of the liver, stomach, nose, and throat (Yang et al., 1993).
- In various *in vitro* and *in vivo* models, PSK could suppress pulmonary and rat hepatoma metastasis, human prostate cancer, lyphatic metastasis of mouse leuke-

mia, and mouse colon cancer, prolonging the survival time in spontaneous metastasis models (Kobayashi et al., 1995).
- PSK eliminated both primary and metastatic tumors in the double grafted tumor system in mice, and was more effective in the model than lentinan or a fraction from *Agaricus brasiliensis* (=*A. blazei* ss. Heinem.) for eliminating both. PSK eliminated both primary and metastatic tumors in a similar model by inducing a sequential antitumor immune mechanism, while a fraction from *A. brasiliensis* had a direct cytotoxic effect on primary tumors only (Ebina, 2003a,b).
- Oral PSK could increase the number of Peyer's patches and led to an enhanced mitogenic lymphocyte response from gut-associated lymphatic tissue in tumor-bearing mice (Matsunaga et al., 1987).

Tumor Cell Killing Effect
- PSK could up-regulate nitric oxide synthase gene expression and production of nitric oxide in mouse PMNs, but not enough to stimulate killing of tumor cells in mice *in vitro* (Asai et al., 2000).
- Although the PSK and PSP inhibit proliferation of some human cancer cell lines (Yang et al., 1992a; Iguchi et al., 2001), not all cancers respond to Tv polysaccharopeptides (Wang et al., 1986; Dong et al., 1997).

Inhibition of Carcinogenesis
- Oral administration of PSK as 10% and less of rat feeds suppressed carcinogen-induced cancers of the colon, esophagus, breast, and lung (Tsukagoshi et al., 1984).

Antioxidant Effects
- Kobayashi et al. (1994) demonstrated that PSK (polysaccharide Kureha) could ameliorate oxidative stress in tumor-bearing rats. Administration of PSK (50 mg/kg, i.p.) 12 days after tumor development caused superoxide release from red blood cells to rapidly decrease. The authors also reported that in colon and gastric cancer patients in whom oxidative stress was found to be twice that of healthy individuals, PSK (3 g/day, p.o.) caused oxidative stress levels to fall to low levels; however, after 7 days patients showed reduced SOD levels and increasing lipoperoxide (LPO) levels. Therefore, the authors suggest that PSK should only be administered to cancer patients for a period not exceeding 7 days, that treatment should begin 7 days before chemotherapy, and that to prevent damage produced by anticancer agents in the form of oxygen free radicals, PSK should be administered in combination with these agents while monitoring superoxide radical levels.

Apoptosis
- *In vitro* studies reveal that PSP acts selectively on HL-60 leukemic cells, arresting the cell in the G-phase of the cell cycle and inducing apoptosis (Hsieh et al., 2002).
- PSK dose dependently stimulated apoptosis in human pancreatic cancer cell line NOR-P1 induced by 1 nM of docetaxel through the NF-kappaB activation pathway (Zhang et al., 2003).

Antiproliferative Effect
- PSP was effective at inhibiting the proliferation of breast cancer cells when they were incubated for 7 days. PSP increased p21 expression and decreased cyclin D1 expression which was used to partly explain the effect of PSP on apoptosis as measured by the TUNEL assay (Chow et al., 2003).
- PSK/PSP has controlled various carcinomas in experimental animals and humans (Ng, 1998). PSP is active against Ehrlich ascites carcinoma, P388 leukemia, and Sarcoma 180 (Yang et al., 1992a).
- A fraction further refined from the total polysaccharide-peptide crude powder of Tv inhibited the proliferation of a human hepatoma cell line, dose-dependently (Dong et al., 1996).
- Other work (Dong et al., 1997) has not found antiproliferative effects of *T. versicolor* polysaccharopeptides against HL-60 human leukemic cells.
- Dong et al. (1996) observed that *T. versicolor* polysaccharopeptides dose-dependently inhibited the proliferation of a human hepatoma cell line (HEPG2), but not the normal human fetal hepatocytes.
- In nude mice, the progression of Sarcoma 180 was measurably reduced by the administration of polysaccharopeptides (Dong et al., 1996).
- Data obtained *in vitro* and *in vivo* suggest that PSP can slow the progression of murine H238 tumors (Mao et al., 1996).
- An intriguing feature of this compound is that injection of PSK at one tumor site has been shown to inhibit

tumor growth in other sites, thus helping to prevent metastasis (Ebina and Kohya, 1987).
- Increased metastatic foci in mice subjected to rotational stress before, during, and after tumor cell implantation and the associated reduction in NK cell activity was significantly reversed by early administration of PSK (Ishihara et al., 1999).
- Other *in vitro* tests showed that PSK inhibited proliferation and invasion of human KATO-3 gastric and Colo205 colonic cancer cell lines and enhancement of HLA class-1 expression on tumor cells (Iguchi et al., 2001).

Anti-Invasion Activity
- PSK could suppress tumor cell invasiveness by downregulating invasion factors TGF-β1, μPA, MMP-2, and MMP-9 in two human tumor cell lines, pancreatic cancer cell line (NOR-P1) and gastric cancer cell line (MK-1P3). PSK did not affect viability, proliferation, or adhesion of the cell lines (Zhang et al., 2000).

Angiogenesis, Inhibition
- PSK could inhibit the proliferation of human umbilical vein endothelial cells at 10 μg/mL and basic fibroblast growth factor (bFGF)-induced angiogenesis *in vivo*, suggesting that PSK binds to bFGF, interfering with bFGF-induced endothelial cell prolifeation, which can inhibit angiogenesis (Wada et al., 2002).

Tumoricidal Activity, Cytotoxicity
- Unlike the higher molecular weight (ca. 100k) PSP, a small polypeptide (SPCV) isolated from Tv demonstrated significant cytotoxic effects on human tumor cell lines (IC_{50}, 30 μ/mL), inhibiting growth of leukemia cells at a significantly higher rate than PSP. SPCV also increased WBC and IgG levels (Yang et al., 1992).
- Neither tumoricidal activity or cytotoxicity could be seen when 5 tumor cell lines were cultured in a solution with 2.5 to 10 μg/mL PSP, however, PSP activated the transcription of tumor necrosis factor gene from cultured peritoneal macrophages in the same culture (Liu et al., 1993).
- PSK significantly inhibited growth of, and demonstrated a cytotoxic effect in 4 human cancer cell lines from the colon, stomach, liver, and pancreas, inhibiting DNA and RNA syntheses in a colon cancer cell line at 10 mg/mL (Takeda et al., 1997).

Anti-Metastatic Activity
- PSK inhibited several mechanisms of cancer cell metastasis. *In vivo*, it suppressed spontaneous lung metastases of melanoma cells in mice. *In vitro*, PSK inhibited chemotaxis of the tumor cells, reduced tumor cell adhesion and haptotaxis to components of the basement membrane (Matsunaga et al., 1996).

P53 Modulation
- PSK administration was able to delay the increase of p53 expression after radiation stress in mouse embryo cells, which coincided with an associated decrease in mitosis and increase in apoptosis, perhaps contributing to an antiteratogenic effect (Kagohashi et al., 2002).

Immunoprotective Effect During Radiation and Chemotherapy
- PSP could significantly augment radiation-induced damage to C6 glioma cells *in vitro*, and tumor volumes were consistently reduced, compared with non-treated controls given only radiation treatment. PSP given with radiation treatment did not increase efficacy of the radiation, but NK cells, lymphocyte and granulocyte counts in the blood and spleen were significantly higher in PSP-treated animals, demonstrating its immunoprotective effect (Mao et al., 2001).

ANTIVIRAL, ANTIBACTERIAL, AND ANTIFUNGAL EFFECTS

In several *in vitro* experiments, PSK was found to inhibit reverse transcriptase and binding of HIV with lymphocytes (Hirose et al., 1987) and block the cytopathic effect of HIV through inhibition of giant cell formation as well as HIV-specific antigen expression in MT-4 and MOLT-4 cells (Tochikura et al., 1987); and inhibit cell-to-cell infection of HIV-1 and HIV-2 and HTLV-I (Tochikura et al., 1989).

Both normal and T-cell-deficient athymic mice were protected by PSK administration from murine cytomegalovirus infection, but the treatment had little effect on NK- and T-cell-deficient mice. Both NK-cell and T-cell activity were seen as necessary for the mice to overcome cytomegalovirus infection (Okada and Minamishima, 1987).

PSK was able to inactivate the infectivity of HSV-type 1 (HSV-1) and HSV-type 2 (HSV-2) from patients with herpes genitalis. HSV-1 and HSV-2 from the patients was inactivated by PSK, dose-dependently after 30–60 minutes. PSK might be clinically useful for inactivating HSV in peripheral lesions (Monma et al., 1997).

When given i.p., Tv extracts could increase host resistance to bacterial and fungal infections (Chu et al., 2002). PSP had little to no antibacterial effects directly (Ng et al., 1996), but did have antibacterial effects through stimulation of host defense.

PSK has also demonstrated antiviral activity. It may inhibit HIV infection by modifying the viral receptor or by stopping HIV from binding with lymphocytes (Tochikura et al., 1987). PSP could inhibit the interactions between HIV-1 gp120 and immobilized CD4 receptor in a series of *in vitro* assays (Collins and Ng, 1997).

Another mechanism through which PSK is reported to have general antiviral activity is through the stimulation of interferon (IFN) production (Ebina et al., 1987).

PSK had a pronounced protective effect against lethal infection with *Candida albicans* in mice. The maximum effect occurred when the PSK was injected at 250 mg/kg i.p. 24 hours before inoculation of 1×10^6 *C. albicans*. A 30-day survival rate increased by 60%, and mean survival time increased by 209%. Both the $\beta 1 \rightarrow 3$ glucan and the protein moiety were seen as necessary for maximum activity (Ohmura et al., 2001).

The resistance and survival time of tumor-bearing mice challenged with *Candida albicans* infection was increased with oral administration of PSK. A significant reduction of fungal counts was also noted (Ohmura et al., 2003).

The action of PSK appears to be through NK cell activation against lethal cytomegalovirus infection (Ebihara and Minamishima, 1984).

Nitrogen-containing polysaccharides extracted from *Ttrametes versicolor* mycelia increased antibacterial potency and prolonged antibacterial effects of antibiotics and can increase antibiotic sensitivity in antibiotic-resistant bacteria (Kureha Chemical Industry Co., 1978).

PSK could inhibit B-cell growth and activate T and NK cells in Epstein-Barr virus (EBV)-infected umbilical cord blood lymphocytes in the absence of EBV-specific immunological memory, exerting enhanced cytotoxicity against EBV-infected B cells (Liu et al., 2002).

HEPATOPROTECTIVE EFFECTS

PSK supported hepatic function (Ito and Hidaka, 1980b) and the possible prevention of liver cancer (Wang, 1989). Two polyoxygenated ergosterol derivatives showed cytotoxicity (*in vitro*) against hepatoma cells (Valisolalao et al., 1983).

PSP given to rats for 7 days (300 mg/kg/day, i.p.) reduced binding affinity of [14C]-paracetamol to liver microsomes by 25%, and significantly reduced serum glutamic-oxaloacetic transaminase levels, but did not reverse depletion of glutathione after a toxic dose of paracetamol (Yeung et al., 1994).

CARDIOVASCULAR EFFECTS

A glycoprotein obtained from the mycelia of *Trametes* spp. showed activity (in animal and *in vitro* tests) against experimental hypertension and thrombosis. The protein inhibits blood platelet aggregation and is analgesic, antipyretic, antihyperlipemic, antiarrhythmic, anti-inflammatory, and vasodilating. It has also been shown to reverse conditions associated with nephron disorders, improve proteinuria and proteinemia-associated conditions, and regulate prostaglandin formation and degradation (Ikuzawa et al., 1985).

PSK (i.p.) could induce peritoneal macrophage colony-stimulating factor (M-CSF) gene expression, as well as protect macrophages from oxidative injury, reducing their transformation to foam cells in the process of atherogenesis, which was related by researchers (Yuan et al., 1996) with its previously demonstrated ability to prevent the progression of atherosclerosis in hypercholesterolemic rabbits. This could be partly due to its ability to enhance superoxidedismutase (SOD) activity and improve glutathione peroxidase activity through induction of mRNA transcription (Pang et al., 2000a,b).

Whole *T. versicolor* has been shown to lower serum cholesterol in animals (Yagishita et al., 1977).

PSK can inhibit ox-LDL-induced macrophage apoptosis and promote NO-induced macrophage apoptosis; Raw264.7 macrophages can be induced to express iNOS mRNA when stimulated with PSK, IFN-γ, and LPS *in vitro*; PSK can enhance the effects of IFN-γ and LPS and suppress the inhibitory effects of ox-LDL. The prevention and treatment effects of PSK on atherosclerosis may be realized by its induction of iNOS (Wang et al., 2001).

Miscellaneous Effects

A powdered extract (from a 70% ethanolic tincture) of *Trametes versicolor* was tested in rats by injection in a Hippocratic screening of higher fungi and demonstrated mild tranquilizing and diuretic activity (Malone et al., 1967).

An analgesic effect of PSP i.v. was noted in three different pain models in rats in acute and chronic inflammatory pain (Teng et al., 2002) and could be mediated by IL-2 activation (Gong et al., 1998).

HUMAN CLINICAL STUDIES

Cancer Adjuvant Treatment

Although some of the studies are small and of uncertain methodology according to recent international standards, starting in the early 1970s, a sufficient number of human clinical trials, along with the mass of preliminary *in vitro* and *in vivo* research showing a broad sprectrum of immunomodulating, antitumor, and anti-metastatic effects, have been performed to give PSP and especially PSK (and perhaps by association *Trametes versicolor* water extracts in general, which contain the fractions) an air of credibility, especially as adjuvants in cancer treatment protocols along with chemotherapy.

The Japanese government has approved these and a few other mushroom extracts—for instance from *Lentinus edodes*—as adjuvant drugs for the treatment of specfic cancers (resected gastric cancer and colorectal cancers and for palliation of small cell lung cancer) as long as it is administered in combination with chemotherapeutic agents (Sugiyama et al., 2002). Much of the antitumor activity proposed for PSK has been elucidated sufficiently on a molecular and genetic level, based on numerous *in vitro*, *in vivo*, and human studies; yet many oncologists in Japan still lack confidence in its efficacy. They are often prescribed and paid for by national health care.

It has been suggested in the literature that, all other things being equal, some patients respond to PSP and PSK better than others. Some intact immune function has been shown to be a positive factor, and in one trial, HLA B40-positive antigen status was associated with an increased survival in breast cancer patients, as compared to B40-negative status, when both groups were given PSK along with conventional chemotherapy (Yokoe et al., 1997). In another study, HLA-A2-antigen-positive status was associated with a better response to postoperative administration of PSK than to chemotherapy and was said to be a predictor for PSK-responsive patients (Ogoshi et al., 1997).

In one study (Sugimachi et al., 1995), lymphocytes from 36 patients with gastric cancer and 26 with colorectal cancer were examined. The PSK-reactive group, 52.8% for gastric cancer patients and 50.0% for colorectal cancer, was defined by a 1.3-fold increase in ^{3}H-thymidine uptake in the lymphocytes. The researchers that the proceedure outlined in this study might help identify "responders," increasing the effectiveness of treatments with mushroom extracts.

Other questions—such as the most effective dose of PSK; the best type of extract or whole mushroom powder; perhaps whether an extract of the whole fruiting body is less, more, or as effective than PSK or PSP; and the frequency of administration—need to be answered through further clinical trials.

In a 1992 study (Nio et al., 1992), 29 patients with gastric cancer and 18 with colorectal cancer were given 3.0 g of PSK before surgery, either daily or every 2 days, or no PSK. The dose frequency made no difference in the outcomes, but in the patients who received PSK for less than 14 days, the response of the peripheral blood lymphocytes (PBLs) to PSK and Con A was stronger than before the start of PSK administration, and in addition, long-term admin-

istration of PSK resulted in reduced activity of the suppressor cells in the regional node lymphocytes (Nio, 1992).

PSK and PSP have been used both orally and intravenously as an immune adjuvant in clinical medicine. PSK has been shown to be effective against many human cancers (Kidd, 2000) but seldom with satisfactory results administered alone.

Cancer patients given 3 g of PSK per day have shown increased interferon production (Ebina et al., 1987a). In cancer patients, PSK also antagonistically elevated the activity of phosphofructokinase and showed antioxidant activity, working as a superoxide and hydroxyl radical scavenger (Nakamura et al., 1986).

Stomach Cancer

Numerous clinical trials were performed in Japan on thousands of patients with stomach cancer, mostly after surgery to remove the cancerous tissue, over the last 30 years, with either chemotherapy alone or with PSK and chemotherapy.

An early controlled clinical trial was started in July, 1974, comparing curative resection surgery alone; surgery with chemotherapy; and surgery, chemotherapy, and PSK in groups with 1412 total patients from 12 medical institutes. Of 848 evaluable patients, the 3-year survival rates were 79.2%, 77.0%, and 85.2% with PSK (Imaizumi et al., 1984), but a later analysis of the data showed less difference. Ten-year survival rates were 67.6%, 64.3%, and 63.9%, which showed no significant difference among the groups (Imaizumi et al., 1990).

Most of the clinical trials summarized in Table 1 showed positive benefits when PSK was added to a long-term chemotherapeutic agent after immediate treatment with chemotherapy. Survival rates after 2–7 years often increased by 10% up to 20%. Some research showed that the best increase in survival times was observed when PSK was alternated with chemotherapy (Nakazato et al., 1994).

In a multicenter trial conducted from 1978 to 1981, 751 patients who underwent macroscopically curative resection for gastric cancer and who took either mitomycin C or futraful (MMC+FT) were compared for preoperative granulocyte and lymphocyte count ratios (G/L). While in the cases with a preoperative G/L ratio of <2.0 no significant difference in survival rates could be seen, in the patients with a G/L ratio of >2.0 the 5-year survival rate of the PSK group ($n = 182$) was 68.7%, while that of the non-PSK group ($n = 182$) was 55.4% ($p = 0.007$) (Nakajima et al., 1989; Toge and Yamaguchi, 2000).

A meta-analysis published in December 1993 reported on six clinical trials evaluating the 5-year survival rate of groups receiving either chemotherapy or chemotherapy plus PSK for patients with advanced gastric cancers. The authors determined that the 5-year survival rate with chemotherapy plus PSK was superior to those receiving the same chemotherapeutic regime alone. The odds ratio was 0.75 (95% confidence interval, 0.62–0.93, $p < 0.01$). Based on a meta-analysis on three further trials starting in 1977, PSK proved to be most effective with patients with T2 and T3 primary tumor subgroups (Sakamoto and Nakazato, 1993).

In a 1994 multicenter randomized but unblinded study involving 262 patients given either a standard regime of chemotherapy or chemotherapy plus PSK at 46 institutions, after curative resection for gastric cancers, PSK improved the 5-year disease-free rate in groups receiving either PSK plus chemotherapy or chemotherapy alone (70.7 vs. 59.4%, $p = 0.047$), and the 5-year survival (73.0 vs. 60.0%, $p = 0.044$) (Nakazato et al., 1994). The PSK patients received oral PSK (3.0 g/day) daily for 4 weeks alternating with oral fluorouracil (150 mg/day) for 4 weeks, and the standard treatment patients received alternating fluorouracil and 4 weeks of rest from treatment. Both groups received 10 courses. Overall, a reduction of about 20% in recurrence and death was seen in the patients receiving long-term oral PSK.

In another study with 224 patients being treated after curative resection for poorly-differentiated gastric cancer, 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and uracil were given, along with PSK in one group and uracil in another group for 1 year. No differences in terms of toxicity rate or outcomes between the two groups was observed. Uracil at 12 mg/kg was the most effective dose (Sugimachi et al., 1997).

TABLE 1. Summary of Clinical Trials—PSK for Gastric Cancer After Curative Resection

Group	No. patients	Institutions	Survival times	Outcomes	Year
Kaibara et al.	66	—	2 yr	MMC and PSK, 2-year survival was doubled over MMC alone.	1976
Fujimoto et al.	230	—	3 yr	Survival rate increased in one subgroup with better intact immune response with PSK.	1979
Hattori et al.	—	—	3 yr	Mitomycin-C (20 + 10) mg after gastrectomy and long-term PSK, FT-207, or (PSK+FT-207); group (P+F) showed best results at 1 year in stage IV, at 2 yr in stage III, and at 3 yr in all stages.	1979
Kano et al.	—	—	5 yr	Mitomycin-C, FT-207, a furanyl analog of 5-fluorouracil, and PSK; survival rates for all stage III and IV patients were 52.8 and 19.3% in PLCC group. Rates were 26.7 and 2.2% in control groups ($p < 0.05$); in curative cases of stage IV, 5-year survival rate was 50.0% in PLCC group and 11.1% in controls.	1981
Hirono et al.	435	—	—	PSK, FT-207 and Levamisole not effective on Borrmann 4-type cancer in 2 randomized controlled trials.	1984
Nakajima et al.	3630	412	3, 4 yr	Most positive results in survival rates was combined therapy (FT + PSK) over single administration (FT) to relatively early stage patients (30%, difference); PSK, MMC, FT combination (10%) and PSK, OK, MMC, FT (22%).	1985
Kanabe et al.	58	—	2 yr	Mitomycin-C + FT 207 + OK 432 + PSK (29 cases) and chemotherapy Mitomycin-C + FT 207 (29 cases); survival rate of PSK group was higher than chemo group throughout observation period, statistical significance in some periods; 50% survival rate was 10 mo in chemotherapy group and 18 mo in immunochemotherapy group.	1985
Nakazato et al.	168	22	2 yr	Carboquon (CQ) dose 2 mg/m2 once a wk, then PSK 2 g/m2 daily for 4 wk. Group A: CQ intermittently; Group B: CQ PSK in alternate doses; Group C: controls. Survival rate of stage III stomach cancer patients in Group B was higher than in Group A, the difference being statistically significant between 20 and 24 mo after surgery.	1986
Ichihashi et al.	—	16	7 yr	Retrospective survival analysis on separate subgroups S1, S2, N1, and N2. CQ + PSK group was better than CQ-alone group in survival rate for S1 + S2 (N1-2) group by 11.5%, and a statistically significant difference was observed between the two groups ($p = 0.089$).	1987
Niimoto et al.	579	97	5 yr	On stratification, MMC + FT + PSK group showed the best survival rate in cases with positive lymph node metastases, positive serosal invasion, and positive lymph node metastases plus serosal invasion, and in cases of undifferentiated carcinoma by histological type and in those with a preoperative positive PPD reaction ($p < 0.01$ or $p < 0.05$).	1988
Nakazato et al.	262	46	3 yr	Disease-free survival curves and overall survival curves of group with PSK were significantly ($p = 0.018$ and $p = 0.045$) better than those receiving chemotherapy alone.	1989
Maehara et al.	255	—	15 yr	15-year survival rate was 45.7% for patients in no-chemotherapy group and 56.9% for chemotherapy group; most significant for patients with ps(–)n(+) ($p < .05$) and ps(+)n(–) ($p < .05$).	1990
Kondo et al.	103	103	7 yr	Patients with S1 + S2 (N1–2) disease survived significantly longer when treated with combination CQ and PSK.	1991
Sakamoto et al.	229	—	2 yr	Disease-free survival improved with PSK when preoperative IAP was lower than 580 μ/mL.	1992
Nakazato et al.	262	46	5 yr	Disease-free 70.7 vs. 59.4%; survival rate 73.0% vs. 60%.	1994
Osawa et al.	185	16	5, 10 yr	5- and 10-year survival rates were 9.8 and 3.1% (PSK without fluorouracil) and 11.1 and 11.1% (with fluorouracil) ($p = 0.062$).	1996

Chemotherapeutic agents included 1-(2-tetrahydrofuryl)-5-fluorouracil (Uracil), 1-(2-tetrahydrofuryl)-5-fluorouracil (Tegafur), Mitomycin C (MMC), 5-fluorouracil (5-FU), Levamisole, and carbazilquinone (CQ), futraful (FT).

Abbreviations: prognostic serosal (ps) invasion [ps(–) or ps(+)] and lymph node metastasis [n(–) or N(+)] was examined.

Lung Cancer

Non-small cell lung cancer (NSCLC) is a common cause of cancer death, and patients often present at advanced stages.

Radiotherapy plus PSK was more effective than radiotherapy (RT) alone for increasing the 5-year survival rate in 185 patients in studies performed from 1976 to 1985. The rate in patients with stage I or II disease with PSK was 39%, and without was 16%. With stage III disease, the survival rates were 16% and 5%. The difference was statistically significant (Hayakawa et al., 1993). The group looked at the same patient population but with the 170 patients with squamous cell carcinoma. They were given PSK only when tumor shrinkage was deemed satisfactory after RT. Compared with the responders to RT that didn't receive PSK, the 5-year survival rates with patients with stage I–II or stage III disease was 39% and 26%, and with no PSK, 17% and 8%, which was statistically significant (Hayakawa et al., 1997).

In a double-blind, placebo-controlled randomized study, 38 patients who had completed conventional treatment for advanced NSCLC were given either PSP or a placebo for 28 days. A significant increase in blood leukocyte and neutrophil counts, serum IgG and IgM, and body-mass index was seen in the PSP patients, compared with those receiving placebo. Significantly fewer PSP patients were withdrawn because of disease progression than their controls (5.9 and 23.5%, respectively; $p = 0.04$). Patients receiving PSP did not report significant adverse reactions (Tsang et al., 2003).

Colorectal Cancer

A number of positive new studies with PSK in combination with various chemotherapeutic regimes are encouraging. In a randomized controlled study the survival of 124 patients in a PSK group plus chemoterapy for 1 year after surgery was slightly better than with chemotherapy alone (91.4% and 80.8%, which was not significant), but the 2-year recurrence rate was lower in PSK groups (Takashima et al., 1988).

In a randomized, controlled study with 462 curatively resected colorectal cancers, PSK was given orally for over 3 years following mitomycin C (by i.v. on the day of surgery and 1 day following) and 5-fluorouracil (5-FU) orally for 5 months. At the time of reporting, the average study follow-up was 4 years. The increased disease-free survival curve of the PSK group over the control group (who only received the two drugs) was statistically significant (Mitomi et al., 1992).

In a similar study, PSK was administered after the same chemotherapeutic regime as the previous study to 56 patients and a placebo to a group of 55 control patients. The rate of remissions and the survival rate in the patients taking PSK was significantly higher ($p < 0.05$) than the control group. Enhanced immune functions, including enhanced polymorphonuclear leukocyte activity, was said to be a significant factor in explaining the results (Torisu et al., 1990).

In a more recent study, the 3-year survival of 48 curatively resected patients diagnosed with colorectal cancer (pTNM stages II and III) receiving fluoropyrimidine plus 3 grams of PSK daily for an average of 11 months was significantly better than in 10 patients receiving chemotherapy alone (Kudo et al., 2002).

PSK, along with cisplatin and UFT, was given to 10 patients with advanced colorectal cancer who had distant metastasis in the liver or lung for 2 months. Serum levels of sIL-2R and IL-10, previously shown to be elevated in patients with advanced colorectal cancer, were reduced (Shibata et al., 2002).

In 27 patients with digestive cancers and 9 healthy volunteers, an analysis of MHC class II+ monocytes and monocytes producing IL-10, MCP-1, and IL-12 was performed before and after daily oral doses of PSK (3 g/day for 7 days). MHC class II+ monocytes declined with cancer progression, and IL-10 and MCP-1-producing monocytes were much higher in patients (M2-dominant status) with advanced cancer than on healthy patients. IL-10 and MCP-1-producing monocytes decreased significantly after PSK. PSK administration might be useful for counteracting the M2-dominant condition common in patients with digestive cancers, improving the balance between Th1 and Th2, which

indicates impaired cellular immune status (Hazama and Oka, 2002).

PSK plus 5′-DFUR chemotherapy for 1 year was only slightly better at increasing overal survival in a group of patients with stage II and III colorectal cancer after surgery with a follow up time of 6.5 years (Koda et al., 2003), but in another randomized controlled study with 446 patients with primary colon cancer after surgery, 10 courses of oral PSK (3 g/day) followed by oral 5-FU significantly increased the survival from cancer deaths, but not the 7-year overall survival rate from all causes (Ito et al., 2004).

In 201 stage II or III colorectal cancer patients with prior surgery, oral PSK plus tegafur/uracil for 2 years following mitomycin treatment, the 3-year disease-free survival rate was 80.6%, compared with 68.7% in the control group receiving only chemotherapy. For stage III patients, the respective values were 83.0% and 59.3%. PSK was more effective for preventing distant metastases, especially lung metastases (Ohwada et al., 2003). After an extended followup with the same patient group, the patients receiving oral PSK (3 g/day) and chemotherapy daily for 2 years had a 5-year disease-free survival rate of 73% (stage II, $n = 123$) and 58.8% (stage II, $n = 68$); the recurrence rate was reduced by 43.6% and mortality by 40.2% in the PSK group, and the 5-year survival was 81.8% in the PSK group and 72.1% in the control group. Notably, the disease-free and overall survival in the PSK group in stage III patients was 60.0% and 74.6%, compared with 32.1% and 46.4% in the control group (Ohwada et al., 2004).

Hepatic Cancer

PSK, lentinan, or no mushroom extract with antitumor drugs administered in a group of 58 patients with hepatocellular carcinoma along with either percutaneous ethanol injection or transcatheter arterial emobolization made no significant difference in mean survival time, mortality rate, time to progression, or T4/T8 lymphocytes (Suto et al., 1994).

Type IV collagen serum levels were measured as a marker for metastasis of hepatic and gastrointestinal cancers and found to be significantly elevated in the group receiving the chemotherapy alone, compared with the group receiving chemotherapy plus PSK up to 12 months after surgery. The 3-year survival rate for patients with colorectal cancer stages II and III receiving chemotherapy plus PSK was significantly higher than in those receiving chemotherapy alone (Kudo et al., 2002).

Nasopharyngeal, Esophageal Cancers

PSK was tested as an adjuvant immunotherapy in a group of patients with carcinoma of the nasopharynx ($n = 21$) and found to significantly increase (35 vs. 25 months) the median survival time over the control group ($n = 17$) as well as the 5-year survival rate (28% vs. 15%). All patients in both groups had previous radiotherapy with or without chemotherapy (Go and Chung, 1989). An earlier study of nasopharyngeal carcinoma patients ($n = 67$) reported similar results (Chung et al., 1987). The dose was 1 gram, 3 times daily, for a minimum of 1 month. Three cases of toxicity were noted.

Among 174 patients with esophageal cancer that underwent esophagectomy, the group receiving radiotherapy (RT) and chemotherapy (CT) plus PSK had better survival times than seen in a group receiving RT and CT, but the outcome was not statistically significant (Ogoshi et al., 1995a). The results were, RT, RT + PSK, RT + CT, and RT + CT + PSK were 40.0%, 42.3%, 29.1%, and 37.2%, respectively. However, when postoperative serum levels of α-1-antichymotrypsin and sialic acid were abnormal, the survivability benefit for patients receiving PSK was statistically significant (Ogoshi et al., 1995b). The authors indicate that levels of the preoperative markers α–1-antichymotrypsin and sialic acid could help identify PSK responders.

PSP increased the rate of remission in esophageal cancer patients to 72% when it was added to chemotherapy, whereas those on chemotherapy alone had a remission rate of 42%. PSP also raised the 1-year survival rate for this type of cancer by 11%. The main immunologic pathways activated by PSP to inhibit tumors are through helper T cell, NK cell, and complement C3 (Yang et al., 1992, 1993).

Uterine Cancer

In a group of 34 patient volunteers with squamous cell carcinoma of the uterine cervix, 21 received either 3 or 6 grams PSK daily combined with radiation therapy. The patients in the PSK groups had less giant cell formation and an increased lethal damage to tumor cells. PSK was most effective in patients whose tumors were radioresistant (Hayashi, 1988).

In combination with radiation in stage III uterine cervical cancer patients, PSK (3-6 g/day) prolonged the life span and appeared to have enhanced the sensitivity of the cancers to radiation therapy. One study performed at the Department of Gynecology, National Cancer Center Hospital in Tokyo (Kasamatsu, 1982), tested the influence of PSK on the survival rate with cervical cancer patients. PSK was given orally in the dose of 3-6 grams a day in conjunction with radiation therapy. After radiation, patients having no observed tumor cells remaining was 36% with PSK and 11% without. The 2-year survival rate was 94% with PSK and 74% without; the 3-year survival rate was 85% and 59%; the 5-year survival rate 64% and 41%. The rate of cancer deaths within 5 years was 21% with PSK and 52% without.

Breast Cancer

In a study that spanned 1980 through 1990, 227 patients with operable breast cancer, vascular invasion in the tumor, and/or metastatic lymph nodes were randomized into chemotherapy (CT), CT plus Levamisole, or CT plus PSK. While the risk ratio was lower in the PSK group, no statistical difference was seen in the disease-free survival or overall survival between the three groups. However, the survival curve of the PSK group tended to be better than that receiving chemo alone ($p = 0.0706$) (Lino et al., 1995).

In a group of 525 patients with stage II estrogen receptor-positive breast cancer, the 5-year overall and relapse-free survival rate did not significantly differ between patients receiving a daily oral dose of 600 mg ftorafur or a daily oral dose of 3 grams PSK, starting 2 weeks after surgery. However, the most effective treatment was tamoxifen plus ftorafur (94.2%), compared with tamoxifen alone (86.9%) or tamoxifen plus PSK (89.9%) (Morimoto et al., 1996).

Among 134 patients with operable breast cancer, patients with vascular invasion in the tumor and/or in metastatic lymph nodes were randomized into two groups. One group received a chemotherapy cocktail with PSK (3 g/day) and one with just chemotherapy. Patients were typed as HLA-A, -B-, C with a lymphocytotoxicity test. The 5- and 10-year disease-free survival rate for patients with B40+ was 100% in both cases, but only 76% and 55% for patients that were B40– (Yokoe et al., 1997).

Leukemia

PSK was given to a group of 73 patients with non-lymphocytic leukemia in complete remission in a randomized cooperative trial. After 6 months, PSK had a borderline beneficial effect on remission duration ($p = 0.089$) and duration of survival ($p = 0.062$). No significant differences in duration of remission and survival between the groups was seen after 12, 18, and 24 months; however, in the patients who did maintain complete remission for more than 270 days, PSK had a suggestive beneficial effect ($p = 0.105$) by prolonging the 50% remission rate by 418 days (885 vs. 467 days).

Miscellaneous Cancers

A controlled double-blind phase II clinical trial of PSP was conducted in 485 cancer patients (211 control patients) treated with the polysaccharide-peptide (3 g/day for 3 0 days p.o.) in combination with radio- and chemotherapies. The patients were diagnosed with cancers of the esophagus, stomach, and lung. PSP reduced side effects from the conventional therapies, with most significant benefits being reduced pain and improvement of poor appetite, tiredness, weakness, and dryness of the mouth and throat. The clinicians noted that in TCM, this indicates an invigorating action on the heart and spleen. Compared to control patients, body weight in the PSP group was significantly higher, and their

T-cell ratio, NK-cell activity, and IL-2 levels were also higher. To counteract the decreases in white blood cell, hemoglobin, and platelet levels that accompany chemo- and radiotherapy, batyl alcohol is often given at the same time. PSP in place of batyl alcohol produced comparable results. Overall, PSP was effective for 82% but only 45% among those also given batyl alcohol ($p < 0.001$) (Liu and Zhou, 1993).

Autoimmune Diseases

Other uncontrolled clinical studies have reported a significant decrease in cyclophosphamide-induced chromosomal damage in children (Tsukagoshi et al., 1984) and fewer sick days and increased immunity in patients with recurrent genital herpes (3–5 g/day) (Kawana, 1985).

Case Reports

When an elderly patient with lier metastiasis from gastric cancer was given CPT-11 (20 mg × 2/day × 2/week) and PSK (3.0 g/day), the tumor was reduced by greater than 50% after 13 weeks of treatment. After 20 weeks the patient reported no adverse effects from the treatment. The researchers suggested that low dose CPT-11 with PSK might produce fewer side effects than the chemotherapeutic agent alone with significant tumor reduction (Takahashi and Mai, 2001).

TOXICITY AND CONTRAINDICATIONS

Unlike many standard anticancer drugs, the PSK in *T. versicolor* produces few, if any, side effects on the bone marrow or other organs, and it shows no immunosuppressive action. In general, *T. versicolor* has very low levels of toxicity and produces few or no side effects (Tsukagoshi et al., 1984). The oral LD_{50} of PSP is reported as 10.0 mg/kg. Negative results were found on the Ames and chromosome distortion tests (Jong and Yang, 1999).

No toxicity or related changes in growth or development was seen in rats and monkeys given PSP for 180 days at up to 12 g/kg daily. ECG and blood chemistry was normal, and no histopathological changes were seen (Zhang et al., 1989). PSP did not affect mouse embryonic development, ovarian steroidogenesis, ovulation, or midterm gestation in mice (Ng and Chan, 1997).

Because of their demonstrated ability to counteract the immunosuppressive activity of cyclophosphamide, PSP and PSK should be avoided during immunosuppressive chemotherapy (Li et al., 1990; Qian et al., 1997).

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