PSK – A potent anti-cancer proteoglycan of the mushroom, *Coriolus versicolor*

Clinical Summary

PSK, a proteoglycan from *Coriolus versicolor*, is an immunomodulator which has been used in conjunction with cancer adjuvant immunotherapy in Japan for decades.

Randomised controlled human clinical trials have documented that PSK has anticancer activity by boosting cellular immune function in the host to defend against tumour progression.

PSK significantly extended disease-free survival at 5 years or more in cancer of the colon-rectum, stomach, oesophagus, nasopharynx, non-small cell type lung cancer, and in HLA-B40 positive breast cancer subjects.

Meta-analysis of randomised controlled trials has confirmed the efficacy of PSK in adjuvant immunotherapy for patients with curatively resected colorectal cancer

PSK significantly enhanced the quality of life and boosted the production of immune effector cells and cytokines to improve immune status in patients with cancer.

PSK is well-tolerated and compatible as an adjuvant immunotherapy with surgery, chemotherapy and/or radiation therapy.

Background

PSK is a proteoglycan concentrate prepared commercially by hot-water extract of cultured mycelia from the edible mushroom *Trametes versicolor*, also known as *Coriolus versicolor or Polystictus versicolor*. The mushroom is also known by the common names of Kawaratake (Japan) and Yun zhi (China) and Turkey tail (Europe and America). Its indications were recorded in the 16th century Compendium of Materia Medica (Vol 28, pp19-21, reprinted by China Press, Beijing) as being beneficial to health and to increase body's defence mechanism.

The substance extracted from *Coriolus versicolor* by hot-water extraction is an active proteoglycan compound known as PS-K in Japan (polysaccharopeptide-Krestin) and PS-P (polysaccharide-peptide) in China. PSK is used as a generic term for PS-Krestin and PS-P, which have the same chemical and structural characteristics.

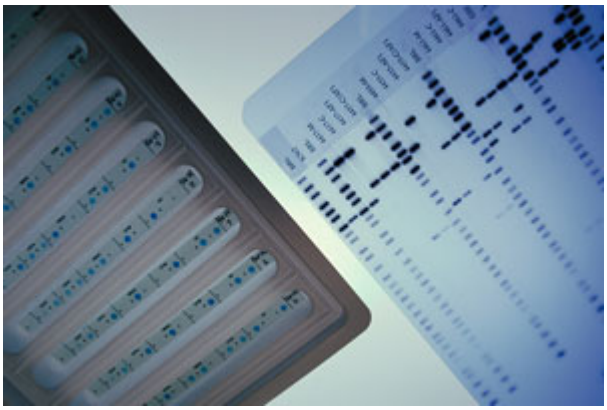
The compound consists of approximately 35% polysaccharides composed of glucose, mannose, xylose, galactose and fucose and 35% protein consisting mainly of acidic amino acids and lesser of other neutral amino acids.[1] The polysaccharides are linked to the core protein (hence the name proteoglycan) to give a beta-1,4-glucan configuration with a molecular weight of approximately 100 kilodaltons.[1,2]

Pharmacokinetics

PSK is highly soluble in water and its bioavailability is by the oral route. Animal testings with radio-labelled PSK show that PSK is partially degraded in the gut to smaller molecules which then appear in the blood within 2 hrs in mice, I hrs in rats and 1-2 hrs in rabbits after oral ingestion. By 4hrs, larger molecules are found in the blood.[3] In cancer-bearing animals, PSK is distributed in the bone marrow, salivary gland, brain, liver, spleen, pancreas and tumour tissues. About 70% of PSK is excreted in expired air while 15-20% is excreted in the urine and 0.8% in the bile[3]. About 11.5% of orally administered PSK accumulates in the macrophages in the liver and spleen.[4] PSK does not interact with other drugs nor affect drug-metabolizing enzyme activities in the liver.[5]

Mechanism of action of PSK

PSK belongs to a class of immunomodulators known as biological response modifiers capable of immunostimulatory and anticancer activities. It induces IL-8 and TNF-α cytokine gene expression in human peripheral blood mononuclear cells from normal healthy subjects and gastric cancer patients given PSK orally.[6]. Peripheral blood CD4+/CD8+ ratio and IL-2 production which were suppressed by chemotherapy were found to increase after oral administration of PSK in patients with ovarian cancer.[7] Oral administration of PSK in older people without disease and patients with malignancy resulted in the restoration of the depressed cellular immunity as determined by the positive Mantoux skin test and skin test reactivity to PHA and endotoxin as well as T cell transformation test *in vitro*.[8] Furthermore, neutrophil functions as determined by chemotaxis and chemiluminescence also increased significantly in patients treated with PSK.[9]. Circulating natural killer cells were found to significantly increase after administration of PSK in subjects with chronic fatigue syndrome.[10]



In patients undergoing radical surgery for cancer, oral administration of PSK prevented surgical stress-induced immunosuppression with a restoration of depressed levels of circulating CD4+ helper T cells, CD8+CD11- cytotoxic T cells and NK cells, and an accompanying reduction in the level of suppressor CD8+CD11+ T cells.[11,12] PSK also activates NK cells and enhances cytotoxic T cell activity in cancer patients.[13,14]

Maintaining the correct balance between cellular (mediated by Th1 helper cells) and humoral (mediated by Th2 helper cells) immunity is critical to the body's ability to mount an effective immune response to infection and human diseases based on the patterns of cytokines secreted.[15] In cancer-bearing state, the balance between Th1 and Th2 immune responses is shifted towards Th2 dominance resulting in poor prognosis. PSK therapy causes a shift of the Th1/Th2 balance towards Th1 dominance in patients with gastric or colorectal cancer,[16] a condition promoting better outcome for cancer therapy.

PSK Clinical trials

Evidence relating to the therapeutic efficacy of PSK comes from numerous clinical trials conducted on thousands of patients in Japan since 1970. To date, significant benefits from PSK immunotherapy used in conjunction with surgery and radiation and/or chemotherapy have been indicated for cancer of the stomach, rectum, colon, oesophagus nasopharynx, breast and lung as demonstrated by the following studies including a meta-analysis. The results showed that PSK given alone or added to chemotherapy or radiation therapy following surgery significantly improved overall survival and disease-free survival.

Colorectal cancer

Positive results have been obtained from randomised controlled single or multicentre trials in patients with advanced colorectal cancer including those with stage II/III diseases.[9, 17-20]
A summary of results from randomised controlled trials for both disease response and survival outcome in patients with colorectal or colon cancer receiving chemotherapy or radiation therapy with PSK is shown in Table 1. The results showed that PSK immunotherapy significantly improved overall survival and disease-free survival rates. For example, as shown by the survival curves (Figs. 1A and 1B), patients with Stage II/III or Stage III colorectal cancer significantly benefited from PSK immunotherapy following surgery.[18]

Table 1. Selected Randomised Controlled Trials for Colorectal Cancer

Ref	Patients	Stage	Treatment	Results
9	55 cases 56 controls	Advance (II/III)	1. Surgery + placebo 2. Surgery + PSK (3gm/day for 2 months; 2g/day for 24 months; 1 gm/day thereafter)	8-yrs survival rate significant in the PSK group($p<0.05$); Disease-free interval ($p<0.05$)
17	Multicentre 221 cases 227 controls		1.Chemo 2.Chemo+ PSK (3g/day for 3 years)	Disease-free interval and survival significantly better for PSK in the colon group ($p<0.05$ in both)
18	Total 207 134 cases 67 controls 6 withdrew	Primary (II/III)	1. Chemo 2.Chemo+ PSK (3g per day for >2 yrs)	Overall survival rate higher in the PSK group but not significant ($p=0.21$). 3-year disease-free survival rate significantly higher in the PSK group ($p=0.02$). Stage III. Patients 3-year overall and disease-free survival rates in the PSK significant ($p=0.02$; $p=0.01$)
19	Total 205 137 cases 68 controls	Primary (II/III)	All patients received Mitomycin-C post-surgery. 1. Chemo 2. Chemo + PSK (3g/ day) Both treatments for 2 yrs	5-year disease-free survival and 5-year overall survival rate significantly higher in the PSK group ($p<0.016$, $p<0.056$ respectively). Stage III patients: Overall and 5-year disease-free survival in PSK group ($p<0.003$; $p<0.002$).
20	Colon cancer with lymph node metastasis Total 441 220 cases 221 controls	Dukes A:7% B:45.5% C:47.3%	All patients received chemo after surgery for 3-4 weeks, then 10 courses of treatment. 1. PSK 4 weeks then 4weeks chemo. 2. 4 weeks rest then 4 weeks chemo.	Seven- year survival rate Significantly higher in the PSK group ($p=0.019$). Overall survival or disease-free rates not significant.

Fig.1A **Survival in Stage II/III Colorectal Cancer**

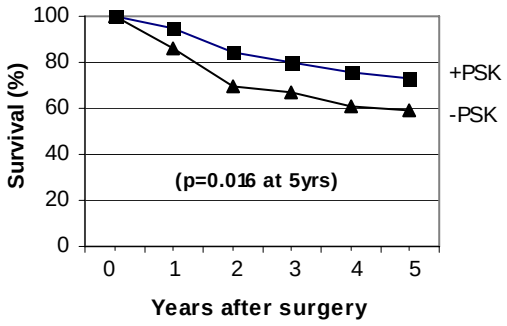
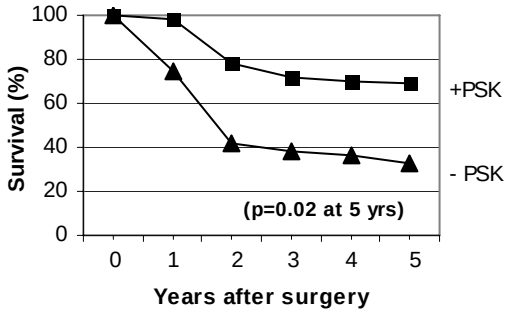


Fig. 1B **Survival in Pathologic Stage III Colorectal Cancer**



A meta-analysis has been performed to evaluate the combined data from three centrally randomised clinical trials for a comparison of the effect of adjuvant immunotherapy using PSK and chemotherapy (n=578) with that of chemotherapy alone (n=516) for 1,094 patients with curatively resected colorectal cancer.[21] All trials had a follow-up for 5-years after surgery and the end-points were overall survival and disease-free survival (Figs. 2A and 2B). The overall survival risk ratio was 0.71 (95% CI: 0.55-0.95, p <0.006) and the disease-free survival risk ratio was 0.72 (95% CI:58-0.90; p <0.003).[21] The results demonstrated that adjuvant immunotherapy with PSK is effective with respect to improved survival and disease-free survival of patients with curatively resected colorectal cancer.

Fig.2A **Five-year Survival in Colorectal Cancer- Meta-analysis**

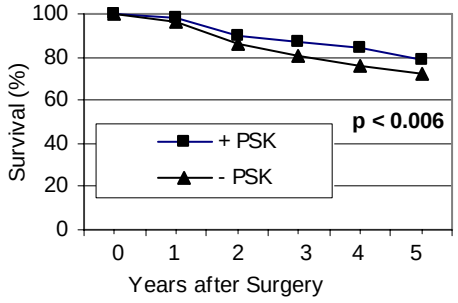
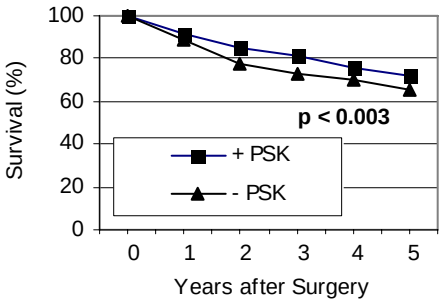


Fig. 2B **Five-Year Disease-Free Survival- Meta-analysis**



Lung cancer

The benefits of PSK to lung cancer patients have been recently demonstrated in more advanced stage III disease where radiotherapy is only marginally effective. In a non-randomised controlled study of stage I/III non-small cell lung carcinoma, patients who responded well to radiotherapy were given PSK (3g/day) for two weeks followed by 2 weeks rest or placebo in 2-week repeated cycles.[22]
The patients (n=62) being given PSK experienced a significant overall improvement in 2-year (36/62(58%) versus 27/123(22%); p<0.0001) and 5-year (17/62(27%) versus 8/123(7%); p=0.0001) survival rates compared to the placebo group (n=123) (Fig. 3A).
When stratified to disease stage and age, patients with stage I/II and stage III epidermoid carcinoma receiving PSK experienced significantly better survival rates (8/22(39%) versus 6/42(16%); p<0.005) and (7/32(32%) versus 2/46(5%); p<0.004) (Fig.3B), respectively than in the placebo groups receiving radiotherapy alone. Furthermore, patients greater than 70 years old who received PSK had better 2-year and 5-year survival rates than those not receiving PSK (p <0.007).

Fig.3A **Survival in Stage I-III Non-small Cell Lung Carcinoma**

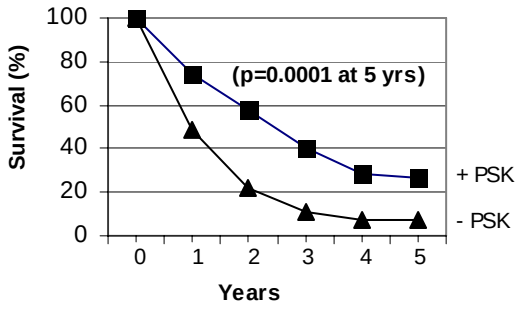
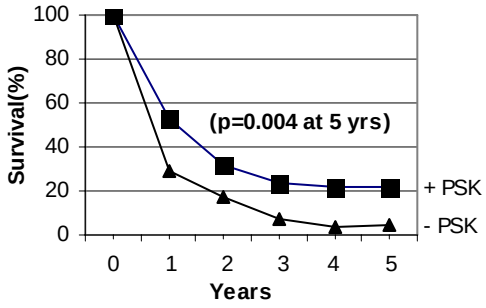
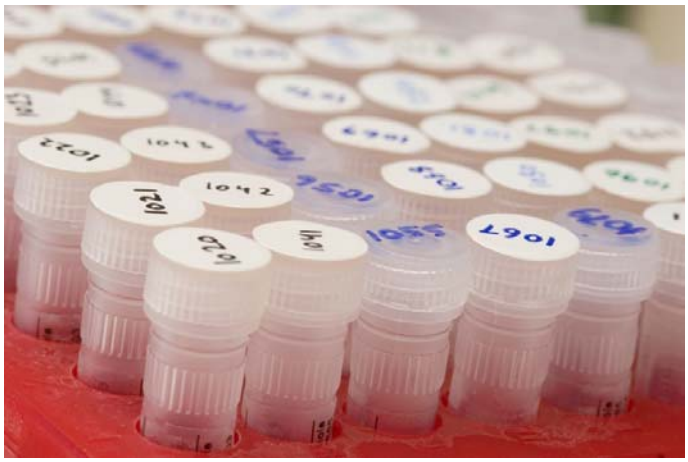


Fig. 3B **Survival in Stage III Non-Small Cell Lung Carcinoma**





Breast cancer

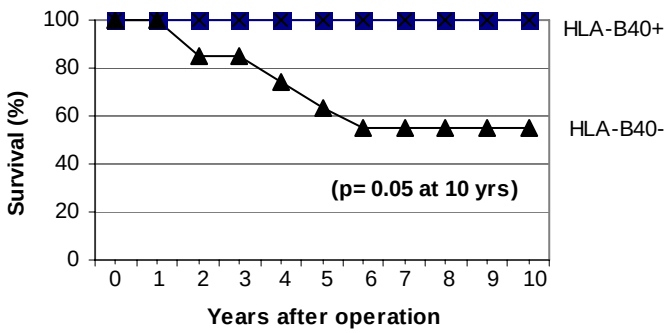
PSK has also been shown to be effective in adjuvant therapy for breast cancer (Table 2). The trials showed a trend towards an improvement in patients treated with chemotherapy plus PSK than those treated with chemotherapy alone although the differences were short of significance.[23, 24] Overall disease survival was also better in the chemotherapy plus PSK but also did not reach significance. However, when the patients were stratified according to HLA-B40 antigen, the results showed that those positive for HLA-B40 had a better survival rate at 10 years than those who were HLA-B40 negative (Fig. 4)(100% (9/9) versus 55% (7/13), $p < 0.05$).[25] It was concluded that HLA-B40 positive patients may benefit greatly from adjuvant immunotherapy with PSK

Table. 2 Randomised controlled trials for breast cancer

Refs	Patients	Stage	Treatment	Outcome
23	914 cases Standard or Radical mastectomy	IIA, IIB, III	1.Patients(ER+tumours) chemo +/- tamoxifen 2.Patients (ER- tumour) Chemo +/- PSK	Longer overall survival for patients in Stage IIA T2N1 cancer ER^- and node-negative treated with chemo + PSK compared with other ER^- subgroups without PSK.
24	227 cases operable breast cancer with v+ and/or n+ involvement		Chemo (n=77) Chemo +LMS (n=76) Chemo +, PSK (n=74)	Risk ratio lower in the chemo+ PSK group. Overall and disease-free survival rates not significant for all groups. **See later published analysis of the HLA-status of these patients below (ref 25)
25	134 cases Typed as HLA-A, HLA-B and HLA-C	Operable with v+ and/or nv+	Previously randomised into two groups(ref 23): 1. Chemo 2. Chemo +PSK Each group stratified by HLA type B40+ or B40-.	Disease-free survival at 5 and 10 Years for chemo + PSK group: HLA-B40+ : 100%; HLA-B40- : 76% and 55%, respectively. Significant difference at p =0.05.

v+, vascular invasion; n+, lymph node involvement; 5-fluorouracil, cyclophosphamide, mitomycin;, prednisolone; LMS; levamisole, ER, estrogen receptor

Fig. 4 **Survival in Breast Cancer Stratified by HLA-B40 Antigen**



Gastric cancer

A well-designed multicentre trial published in The Lancet reported that patients (n=129) with Stages I-IV gastric carcinoma receiving a standard dose of PSK (3g/day) for 4 weeks alternating with chemotherapy for 10 cycles following curative resection of cancer significantly improved both the 5-year survival (73.0%(90/124) versus 60.0%(77/129) p=0.044) and the disease-free survival rates (70.7%(87/124) versus 59.4% (77/129), p=0.047) compared with those receiving chemotherapy only (n=124).[26](Figs. 5A and 5B). The study recommended the addition of PSK to standard chemotherapy for resected gastric cancer.

In a retrospective study of 872 patients with gastric cancer, abnormal serum levels of carcinoembryonic antigen (CEA) and acute phase reactants (APR) were associated with better survival with PSK than those without PSK (29.3% vs 6.9%; p <0.0015).[27] CEA-positive patients receiving PSK therapy showed a significantly better survival rate than those without PSK (38.1% vs 18.6%, p =0.0136).[27]

Fig. 5A **Overall Survival in Gastric Cancer**

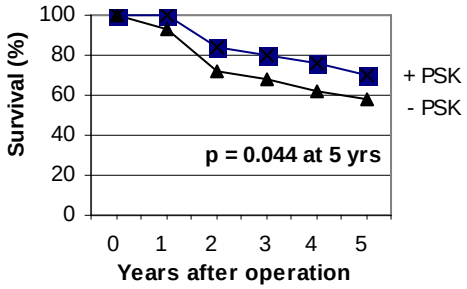
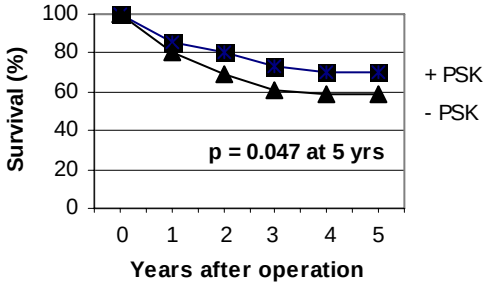


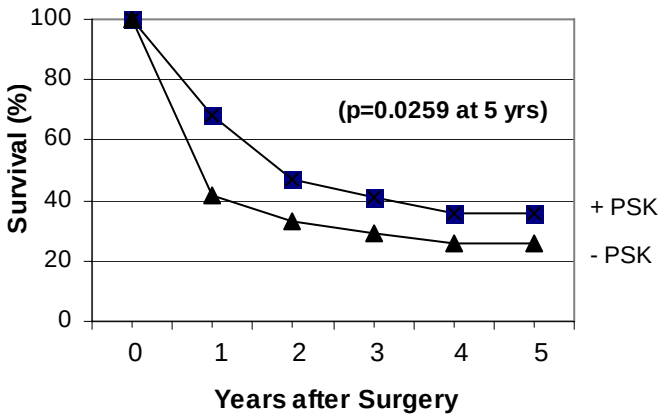
Fig. 5B **Five-year Disease-Free Survival in Gastric Cancer**



Oesophageal cancer

In oesophageal cancer patients (n=158) treated with radiotherapy and PSK (3 g/day) for >3 months, raised serum α−1-anti-chymotrypsin levels were associated with a higher survival rate at 5 years than the control group (55% versus 26%, p < 0.008).[28] Similarly, overall survival 5-years rate was also higher in patients with elevated serum sialic acid levels (58% versus 31%, p <0.07).[28] Overall survival rates of patients treated with radiotherapy and/or chemotherapy with or without PSK were 42.2% (36/85) versus 35.7% (26/73) (p=0.0259) (Fig. 6). There was a significant difference between patients treated with radiotherapy plus chemotherapy(31.5%(13/41) versus radiotherapy plus chemotherapy plus PSK(39.4% (19/49)(p= 0.0404). These results showed that oesophageal cancer patients benefited from radiotherapy and chemotherapy together with PSK especially those with raised serum levels of tumour markers.

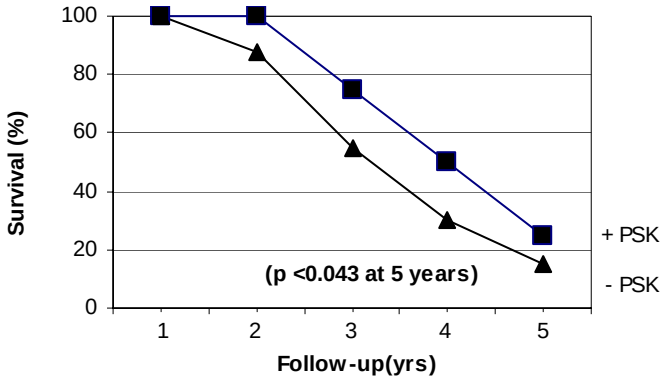
Fig. 6 **Overall Five-year Survival in Oesophageal Cancer**



Nasopharyngeal cancer

In a randomised study of 38 patients with stage I-IV nasopharyngeal carcinoma following standard radiotherapy with or without chemotherapy, there was an improvement in the rate of metastasis in patients given PSK(14% ,3/21) compared with patients in the control group without PSK (35%, 6/17)[29] but the difference was not statistically significant (p =0.24). The median survival (35 months versus 25 months, p<0.043) and 5-year survival rates(28% (6/23) versus 15% (2/17), p<0.043) were significantly better in the PSK treatment group (Fig. 7). It was concluded that PSK may be a useful immunotherapeutic agent in the management of nasopharyngeal cancer.

Fig. 7 **Five-year Overall Survival in Nasopharyngeal Cancer**



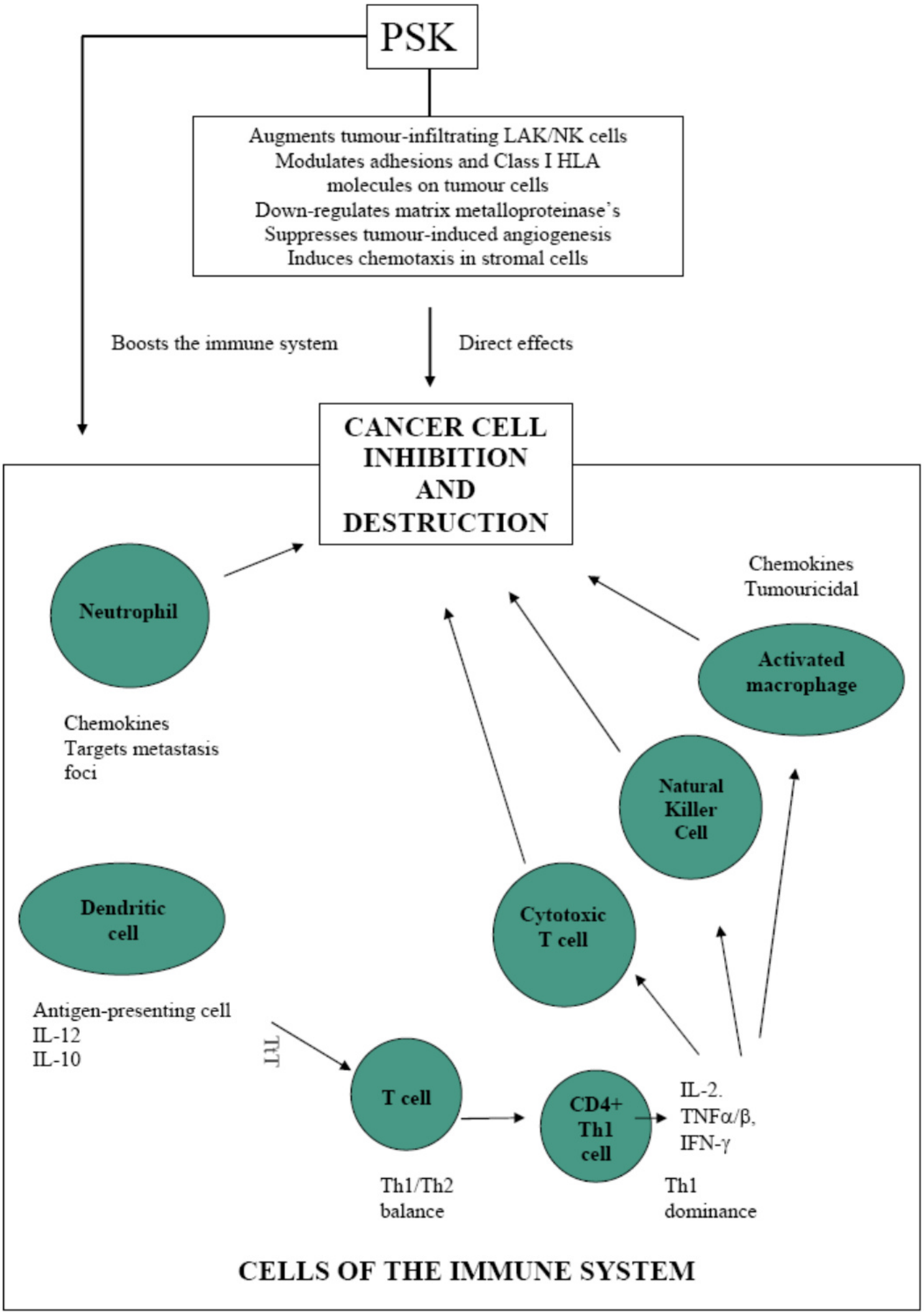
Leukaemia

The addition of PSK to maintenance chemotherapy was found to improve the survival rate of patients with acute myelogenous leukaemia (AML)[30] but this was short of statistical significance (p =0.105). However, patients who remained in remission for 270 days benefited for a further 418 days on PSK.
In another study, PSK was effective in preventing relapse in childhood acute lymphoblastic leukaemia following treatment with chemotherapy but the benefit was also not statistically significant.[31] Although showing no significant effect with PSK, adverse effects were not observed in this paediatric population.

Adverse reactions

Adverse reactions from PSK have not been reported since clinical trials began in Japan since 1970. However, symptoms such as coughing, nail pigmentation, constipation and diarrhoea have been reported.[9,32] These side effects were significantly reduced when PSK was formulated in tablets or capsules instead of the medication given as a powder form reconstituted in water.[9] Low grade gastrointestinal and haematological toxicities have been reported, which may be due to chemotherapeutic agents and radiation themselves.[18,19] The Japanese Ministry of Health and Welfare reported that side effects were experienced in 114 patients of a total of 11,300 cancer patients administered PSK (1.01%).[33] The main symptoms reported were diarrhoea and nausea.

PROPOSED IMMUNOMODULATORY AND ANTI-TUMOUR PATHWAYS OF PSK



Regulatory status

In Japan, PSK is a prescriptive medication for use at a dosage of 3 g per day as an immunoadjuvant therapy agent in combination with chemotherapy, radiotherapy and surgical treatments of colorectal and gastric cancers. Safety evaluations have reported that the product is extremely safe and complied with LD-50 test.

In other parts of Asia, PSK is sold as an OTC product in pharmacies to be taken in 500 mg capsules or as an extract or as a tea. PSK is also marketed in the US as a food supplement or in a class of mushroom 'immunoceuticals' with known immuno-therapeutic properties.

PSK is recorded as an anti-cancer fungal substance suited for treatment regimens used in cancer management by the American National Cancer Research Center[34,35] but has not been evaluated by the Food and Drug Administration.

PSK proteoglycan isolated from a commercial preparation of *Coriolus versicolor*, is now available in Australia.

****IMPORTANT NOTICE****

This review was prepared by PSK Information Foundation, a non-profit organisation which does not have a product for sale. The review for educational purposes was based on information gathered from published studies in scientific journals which are believed to be reputable and reliable. Readers should make their own inquiries to satisfy themselves on all information contained on this website.

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