ABSTRACT. 1. Protein-bound polysaccharides, designated as PSK and PSP, have been isolated from the CM-101 strain and the COV-1 strain, respectively, of the mushroom *Coriolus versicolor*. This article aims at summarizing existing research findings about PSP since information on PSK is well documented.

2. PSP possesses a molecular weight of approximately 100 kDa. Glutamic and aspartic acids are abundant in its polypeptide component, whereas its polysaccharide component is made up of monosaccharides with α-1,4 and β-1,3 glucosidic linkages. The presence of fucose in PSK and rhamnose and arabinose in PSP distinguishes the two protein-bound polysaccharides, which are otherwise chemically similar.

3. PSP is classified as a biological response modifier. It induces, in experimental animals, increased γ-interferon production, interleukin-2 production, and T-cell proliferation. It also counteracts the depressive effect of cyclophosphamide on white blood cell count, interleukin-2 production and delayed-type hypersensitivity reaction. Its antiproliferative activity against tumor cell lines and in vivo antitumor activity have been demonstrated. A small peptide with a molecular weight of 16–18 kDa originating from PSP has been produced with antiproliferative and antitumor activities.

4. PSP administered to patients with esophageal cancer, gastric cancer and lung cancer, and who are undergoing radiotherapy or chemotherapy, helps alleviate symptoms and prevents the decline in immune status.

KEY WORDS. Mushroom, polysaccharopeptide, *Coriolus versicolor*

Mushrooms are known for their nutritional and medicinal value (Breen, 1990) and also for the diversity of bioactive compounds they contain. The mushroom *Coriolus versicolor* (Yun Zhi) was recorded in the *Compendium of Materia Medica* by Li Shi Zhen during the Ming Dynasty in China, as being beneficial to health and able to bring longevity if consumed regularly. Various products derived from this mushroom and claimed to have medicinal value are commercially available. Among them, PSK (Sakagami *et al.*, 1991) and PSP are the most prominent. It is the intent of this article to summarize research data pertaining to PSP.

PSK (Sakagami *et al.*, 1991) and PSP are two chemically related products of the mushroom *Coriolus versicolor* isolated from deep-layer cultivated mycelia of the COV-1 and CM-101 strains, by Chinese and Japanese investigators, respectively. The similarities and differences of the two products have been pointed out by the Fungi Research Institute (1993a). Both possess a molecular weight of approximately 100 kDa and their polypeptide moieties are rich in aspartic acid and glutamic acid. Monosaccharides with α-1,4 and β-1,3 glucosidic linkages constitute the polysaccharide moieties of PSP and PSK. Fucose is found in the former, whereas arabinose and rhamnose occur in the latter. Both PSP and PSK have been found to be immunoenhancing and effective against tumor cells.

Yang and Zhou (1993) are credited with the structural elucidation of PSP. PSP has been subjected to infrared (IR) and nuclear magnetic resonance (NMR) spectroscopic studies. An IR spectrum with absorption peaks at 3400, 1650, 1050 and 893 cm⁻¹ is indicative of the presence of an OH group, an NH₂ group, C–O–C and β-glycosidic linkage, respectively. The major absorption peak at 3.0–4.3 ppm in the NMR spectrum denotes the existence of polysaccharide. The proton resonance signals at 1.0–2.5 ppm and 5.38 ppm signify amino acid side chain and β-linked polysaccharide peptide, respectively. The absorption spectra of PSP and PSK over 230–700 nm exhibit a remarkable similarity to each other, whereas starch does not absorb at this range of wavelengths. Gel filtration of PSP on Sephadex G-100 yields a single peak containing both protein
and carbohydrate. When taken together the above data infer that PSP is a polysaccharide bound to a polypeptide moiety. Analysis of the polysaccharide moiety using gas chromatography/mass spectrometry reveals a predominance of 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.

Yang et al. (1993b) classified PSP as a new biological response modifier which is defined as an agent capable of modifying the host's biological response by stimulating the immune system and thereby eliciting various therapeutic effects (Tomada et al., 1987). PSP exerted immunomodulatory and antitumor activities (Yang et al., 1992). Oral administration of PSP at 1.5 mg/kg to normal ICR mice brought about an elevated production of interleukin-2. ConA-stimulated proliferation of mouse T cells was enhanced by incubation in the presence of PSP at and above 100 μg/ml. Interferon-α production by human white blood cells was also augmented by PSP. PSP could also partially offset the decrease in white blood cells and interleukin-4 production induced by cyclophosphamide injection in mice, and reverse the inhibition of the delayed-type hypersensitivity reaction produced by cyclophosphamide. In addition, it prevented thymus involution and increased production of IgG and complement C₃ in sarcoma-bearing mice (Yang et al., 1993a).

Zeng et al. (1993) reported that oral administration of PSP at 1−2 g/kg per day for 15−20 days to nude mice inhibited growth of human lung adenocarcinoma by 50−70%. Wang et al. (1993) found that PSP administered intraperitoneally (IP) at 50 mg/kg per day for about 3 weeks produced approximately 45% inhibition of the growth of Lewis lung cancer. A reduced inhibition of liver cancer was observed after treatment with PSP. Yang et al. (1993b) noted an inhibitory effect of PSP on incorporation of ³H-thymidine and ³H-thymidine into nucleic acids in Ehrlich ascites tumor cells. PSP exerted a greater inhibitory effect than PSK on P388 leukemia cells. The anti-proliferative potencies of PSP and PSK against human gastric cancer, lung cancer, lymphoma and mononuclear leukemia cell lines were similar. Intraperitoneal or oral administration of PSP likewise inhibited the growth of sarcoma 180 cells in mice, with the former route of administration being more effective. Yang et al. (1993c) purified a small peptide with a molecular weight of 16−18 kDa from a crude preparation of PSP using reverse-phase HPLC. The peptide, designated PCV, suppressed ³H-thymidine incorporation into human leukemia HL-60 cells, colon cancer LS174 T cells, human hepatoma SMMU-7721 cells and human gastric cancer SGC-7901 cells. It also reduced tumor growth in mice in which myeloma cells, leukemia cells or hepatoma cells had been implanted or inoculated. The survival rate of the tumor-bearing mice was higher after PSP treatment. No lesions were produced in the vital organs after prolonged treatment (2 months) with therapeutically effective doses (40 mg/kg) of PCV. In contrast, necrotic changes were detected in tumor cells. PCV treatment increased white blood cell count and serum IgG in mice. An increase in CD4⁺, CD8⁺ β lymphocytes and neutrophils also occurred.

Xu et al. (1993) observed that PSP restored the immune status in cyclophosphamide-treated rats as witnessed in serum IgG titer, lymphocyte proliferation and NK cell function. Xu et al. (1993) noticed an increase in percentage of acidic α-naphthol-acetate-esterase-positive T cells in rats, indicating an increase in immune function.

Liu et al. (1993) did not, however, detect tumoricidal activity when five tumor cell lines, including P388D1 (mouse monocyte-macrophage), B16 (mouse melanoma), S180 (mouse sarcoma), PC17-1.8 (mouse monocyte-macrophage) and JAR (human placental chorioncarcinoma) were cultured in the presence of 2.5−10 μg/ml of PSP. Nevertheless, elevated production of reactive nitrogen intermediates, superoxide anions and tumor necrosis factor was noted in peritoneal macrophages from inbred C57 mice administered PSP in their drinking water for 2 weeks. Northern blot analysis also revealed that PSP stimulated transcription of the tumor necrosis gene in peritoneal macrophages, illustrating the immunostimulatory action of PSP.

Chen et al. (1993) reported that PCV induced tumor regression in some liver cancer patients. Liu et al. (1993) conducted a clinical trial of PSP on patients with lung cancer, gastric cancer and esophageal cancer. Most of the patients were beyond the early stage of the disease. The lung cancer and gastric cancer patients had undergone operation and often chemotherapy as well, whereas the esophageal cancer patients had received radiotherapy. The results were encouraging. There were marked alleviations of the symptoms. A large percentage of patients had put on ≥1 kg of body weight, and a smaller percentage lost ≥1 kg of body weight. The activity of NK cells, production of interleukin-2, CD4⁺/CD8⁺ ratio and white blood cell count increased as a consequence of PSP treatment. Gao (1993) performed a similar study and obtained comparable results. Liu (1993) examined the effect of combined treatment of esophageal cancer with radiotherapy and PSP and found that the decline in the CD4⁺/CD8⁺ ratio following radiotherapy was prevented by PSP treatment. The 1-year survival rate was increased from 50% in patients receiving radiotherapy only to 70% in patients subjected to both radiotherapy and PSP treatment. Wu et al. (1993) also studied the beneficial influence of PSP treatment given concurrently to esophageal patients undergoing radiotherapy. The treatment regimen was similar to that used by Liu et al. (1993); that is, 0.34 g PSP per capsule, three capsules each time, three times a day for 1−2 months. In general, results similar to those of Liu et al. (1993) were obtained, with the finding regarding the CD4⁺/CD8⁺ ratio being the only discordant data.

In gastric cancer patients receiving chemotherapy, Shi et al. (1993) demonstrated that simultaneous PSP treatment increased NK cell activity, CD4⁺ and CD4⁺/CD8⁺ ratio. Xie (1993) showed that PSP, administered to gastric cancer patients operated on to remove their cancers, and receiving chemotherapy, increased red cell immunity as evidenced in the elevated erythrocyte-tumor-cell rosette rate. The NK cell activity and serum interleukin-2 level were heightened. Xu (1993) similarly reported that PSP treatment applied during chemotherapy of gastric cancer brought about an alleviation of symptoms arising from chemotherapy and a strengthening of the immune function, including NK cell activity, interleukin-2 level and CD4⁺/CD8⁺ ratio. Shi et al. (1993) furnished further corroborative data.

Liao and Zhao (1993) undertook a clinical trial of PSP on lung cancer patients, most of whom had passed the early stage of the disease. The patients were on chemotherapy. PSP treatment ensued with an alleviation of symptoms, a stabilization of or an increase in body weight, and an increase in white blood cell count. Blood platelet count, hemoglobin level, interleukin-2 level and NK cell activity. Ke (1993) briefly reported the efficacy of PSP in boosting immunologic function as reflected in NK cell activity and number of lymphocytes and in minimizing the side effects of chemotherapy in lung cancer patients.

PSP given to breast cancer patients receiving chemotherapy caused an increase in appetite and prevented a fall in white blood cell count and platelet count without impairing liver or kidney function (Shiu et al., 1993). PSP has been shown to exert a protective effect against paracetamol-induced hepatotoxicity in the rat (Yeung et al., 1994). It is devoid of teratogenic effects in mice (Ng and
Chen C. N., Yang, M. M. P. and Zhu P. (1993) Research and application of peritoneal exudate cells and mitogenic activity of T cells in tumor-bearing mice and induced gene expression of some immunomodulatory cytokines in mice (Liu et al., 1995, 1996a,b). From a submerged mycelial culture of another Tricholoma species, a peptide-bound polysaccharide with a molecular weight of 17 kDa, which exhibited more potent immunomodulatory and antitumor activities than PSP, was purified (Wang et al., 1995). Another peptide-bound polysaccharide with a molecular weight of 15.5 kDa was prepared from the cultured mycelia of Tricholoma mongolicum (Wang et al., 1995). It possessed the properties of activating macrophages, stimulating macrophage antigen-presenting activity, which in turn enhanced T-cell proliferation, and inhibited the growth of sarcoma 180 cells implanted into mice. Wang et al. (1996a) found that both mouse lymphocytes and macrophages were activated by preparations of polysaccharopeptide from cultured mycelia and culture medium of C. versicolor. Glucans including lentiman and schizophyllan and those extracted from other fungi such as Ganoderma lucidum and Volvariella volvacea are also known to possess immunomodulatory activities. It is hoped that these polysaccharides and protein-bound and peptide-bound polysaccharides can be developed into clinically useful drugs. Evidence has been accumulating that mushrooms have nutritional as well as medicinal value.

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References


