PSK SCIENTIFIC & CLINICAL SUMMARY

Coriolus versicolor (Trametes) - A medicinal mushroom

- A *Basidiomycetes* macrofungi - member of the polyporaceae family
- First use in Traditional Chinese Medicine (TCM) in the Ming dynasty (16th century)
- High therapeutic potential
- Minimal toxicity
- Beneficial effects to general health
- Extracts known to be effective in promoting health of cancer subjects

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Bioactive compounds

- Polysaccharides-K or protein-bound polysaccharides (PSK)
- Basic β-glucan structure with 1–3β- and 1-4β linkages main chain and 1-3 and 1-6-β branch points for every four 1-4 linkages
- High water solubility and present in systemic circulation 2-4 hrs after oral ingestion
- Stable in the blood circulation and distributes in BM, salivary gland, brain, liver, spleen, pancreas and tumour
- Does not interfere with other drugs nor affect hepatic drug-metabolizing enzymes
- PSK reaches the tumour tissue in the active form to exert anti-tumour activity
- Chemical modification of polysaccharide structure can enhance or attenuate antitumour activity

Immunodulatory effects (direct effects on cells of the immune system)

PSK activate cells of the innate immune system that lead to the activation effector T cells.

- Activates the complement system and the thymus
- Enhances pro-inflammatory interferon, IL-1 and TNF-α production
- Enhances macrophage chemotaxis in tumour-bearing state
- Restores T cell function (DTH, cytotoxic T cells)
- Promotes localization of effector cells at tumour site
- Augments NK and LAK cell activity
- Enhances proliferation of CD4+ and CD8+T cells and activated T cells
- Promotes bystander killing of tumour cells by 'PSK'-antigen-specific cytotoxic T cells
- Induces cytokine gene expression in immune and inflammatory cells
- Activates T cells via monocytes/macrophages secreting IL-15
- Reduce immunosuppressive substances in tumour-bearing host
- Mediate anti-tumour activity via antigen-specific mechanisms
- Drives dendritic maturation to induce Th1 dominance
- Augments IL-2 production by gut mucosal CD4+ T cells via modulation of T cell receptor signalling
- Regulates TH1/Th2 balance and regulatory T-cells (Treg)
- Acts as a TLR2 agonist to mediate inhibition of tumour growth and CD8 T cells and NK cells

Cellular and molecular targets

- Mediates NF-κB inhibition to augment drug-induced apoptosis
- Upregulates antioxidant Mn superoxide dismutase, Se-dep glutathione dismutase and glutathione S-transferase.
- Upregulates iNOS and NO production in PMN
- Suppresses CD57(+) T cells to improve survival of advanced gastric cancer patients
- Stimulate TNF-α secretion via activation of TLR4 receptor on macrophages
- Enhances docetaxel efficacy by inhibiting NFκB activation and surviving expression in gastric cancer cells
- Prevents apoptosis of circulating T cells induced by anti-cancer drug
- Inhibits prion activity involved in infectious neurodegenerative disease
- Induce maturation of immune-tolerant dendritic cells in combination with TGF-β receptor I kinase inhibitor
- Prevents apoptosis of circulating T cells induced by anti-cancer drug in patients with gastric cancer.

Chemopreventive and radioprotective effects

- Delays carcinogenic agent-induced carcinogenesis
- Inhibits spontaneous tumour development
- Protects chemo and/or radiation-induced normal cell injury through upregulation of MnSOD
- Suppresses chromatid damage and sister chromatid exchange in bone marrow
- MnSOD expression reduces tumour control radiation dose and tumourogenecity
- Reduces side effects when combined with low-dose chemotherapeutic drug, cisplatin

Direct anti-neoplastic effects

- Sensitises tumour cells (enhaced expression of apoptosis and HLA Class 1) for elimination in the host
- Inhibit tumour cell proliferation via cytokine activities of immune and inflammatory cells
- Alters prostaglandin metabolism and therefore platelet aggregation and vascular adhesion
- Inhibits cytoskeletal function and motility (mobility), and therefore, interferes with extravasation process leading to metastasis
- Inhibits angiogenesis and therefore metastasis
- Mimics SOD activity to enhance sensitivity of tumour cells (for elimination by cancer treatment) whose SOD and coupling enzyme activities are lower than normal cells
- Suppresses tumour cell progression by increasing SOD (via inflammatory cytokine activities by deceasing TGF-β and increasing IFN-γ)
- Binds to TGF-β and PDGF leading to inactivation
- Downregulates matrix metalloproteinases MMP2 and MMP9, uPA expression and TGF-β1 expression to reduce tumour cell invasiveness and metastasis
- Enhances HLA Class I and Class expression to promote immune surveillance and recognition
- Decrease cell growth and PCA production in androgen-sensitive prostate cancer cells
- Augment anti-tumour action by upregulating multi-drug resistance proteins without disrupting cell-cycle progression
- Prevent metastasis when used in combination with anti-cancer agent, docetaxel

Early clinical studies

- Significant benefits when used with standard cancer treatment
- Positive results in cervical, esophageal, gastric, colorectal, bladder, nasopharyngeal and lung cancers as well as medulloblastoma, astrocytomas, oligodenrogliomas and leukemias
- Case reports also shows benefits in malignancies including sarcomas, hepatocellular carcinomas, cholangiocarcinomas, pancreatic carcinomas and ovarian cancers

Randomised-controlled clinical trials

- Use for decades as an adjuvant cancer therapy for the treatment of stomach, colorectal, lung, stomach, breast, esophageal and nasopharyngeal cancers and leukemias
- RCT and meta-analysis confirm extended survival in colorectal and gastric cancers
- Adverse reactions have not been reported
- Symptoms such as coughing, nail pigmentation, constipation and diarrhoea have been reported
- Low grade haematological and GI toxicities have been reported but these may be due to cancer treatment

Other potential uses

Normal tissue radioprotector, tumour radiosensitiser and chemoprotector

- Decreases tumour growth after radiation therapy in mice
- Enhances splenic cell colony formation
- Enhances lymphocyte infiltration into tumours, decreases risk of metastases
- Reduces or prevent radiation-induced congenital malformation and tetratogenic effects
- Increases radiosensitivity of tumours by SOD mimicry or induces expression of SOD and protective effect on normal cell
- Enhances effect of irradiation on carcinoma of the cervix
- Enhances anti-cancer activity of cisplatin
- Mediates NFκB inhibition to augment docetaxel-induced apoptosis in human pancreatic cells
- Reduces myelosuppression of cytotoxic chemotherapy
- Acts to reduce oxidative stress due to free radicals induced by chemotherapy
- Suppresses the increase in lipid peroxide and decrease in SOD activity in normal cell induced by treatment with cisplatin
- Augments lipid peroxide formation and the decrease in SOD in cancer cells induced by cisplatin

Positive predictors of PSK-improved overall survival in cancer patients

- Carcinoembryonic antigen (CEA) levels > 65 yrs
- High NK cell numbers
- Positive delayed type hypersensitivity (DTH) by the tuberculin test
- Abnormal serum IAP levels
- Low CD57(+) T cell numbers
- Nuclear factor-kappa B activation
- Diffuse nuclear accumulation-type beta-catenin activation

Regulatory status

- Prescribed as an adjuvant therapy agent in Japan for cancer treatment at a dose of 3 gm/day
- Complied with LD-50 test
- Marketed in the US as a class of mushroom immunoceuticals
- Lists as a TGA complementary medicine product

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