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Pharmacological Functions of Chinese Medicinal Fungus *Cordyceps sinensis* and Related Species

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ABSTRACT

Cordyceps sinensis, an entomogenous fungus used in traditional Chinese medicine, exhibits very broad biological and pharmacological actions in hepatic, renal, cardiovascular, and immunologic systems as well as anticancer activity. Pharmacological functions of *Cordyceps* are primarily due to the bioactive polysaccharides, modified nucleosides, and cyclosporin-like metabolites produced by this fungus and related species. The beneficial effects on renal and hepatic function and immunomodulation-related antitumor activities are most promising and deserve great attention. Many previous studies used fruiting bodies, but recently an increasing number of studies have used cultured mycelia in investigations. It is difficult to determine if the same bioactive ingredients exist in fruiting bodies and cultured mycelia and contribute to the pharmacological actions reported in the literature. More mechanism-based, disease-oriented pharmacological studies are required to ensure clinical efficacy for particular diseases. Adjuvant therapy using *C. sinensis* for immune function disturbances, cancer, and renal failure is possible if double-blind, randomized placebo-control clinical studies show the efficacy of this herb.

Key words: *Cordyceps sinensis*, anticancer activities, hepatic function, renal function, immunomodulation, polysaccharides, modified nucleosides

INTRODUCTION

Cordyceps sinensis (Berk.) Sacc. (abbreviated as CS) is an entomogenous fungus that has long been used as a Chinese medicine and tonic foods. The herbal product is composed of the fruiting body and its host larva. Many recent pharmacological studies have used fermented mycelial products. CS in its wild form and mycelial products exhibits a broad spectrum of biological and pharmacological actions in hepatic, renal, cardiovascular, immunologic, and nervous systems as well as anticancer activity[(1-3)]. The effects of CS on the renal system and its modulatory effect on the host immune system deserve great attention. Active principles in *Cordyceps* are primarily polysaccharides, modified nucleosides, and cyclosporin-like metabolites produced by this medicinal fungus. According to the physicochemical properties of natural products, aqueous preparations (polysaccharide containing) and alcohol extracts (polysaccharide-devoid) of CS are most commonly used for *in vitro* and *in vivo* studies. Only a few reports use pure compounds from CS for pharmacological studies. In quite a few studies, the origin and taxonomy of *Cordyceps* products are not clearly addressed. This article intends to review the pharmacological functions of CS and related species based on the recent advances in the literature and from our laboratories (Table 1).

PHARMACOLOGICAL FUNCTIONS OF *CORDYCEPS*

Hepatic Function

The mycelial extract of cultured CS stimulates hepatic

Table 1. Major pharmacological functions of *Cordyceps sinensis*

Hepatic function
a. Stimulation of energy metabolism
b. Activation of Kupffer cell function: water-soluble fraction
c. Reduction of post-hepatitic cirrhosis: unknown
Renal function
a. Reduction of aminoglycoside-induced nephrotoxicity
b. Reduction of hematuria and proteinuria in experimental IgA nephropathy (IgAN): low MW sterols (CS-H1-A)
Endocrine and steroid system
a. Stimulation of corticosteroid production in animals: unknown
b. Stimulation of corticosterone production by cultured rat adrenal cells: water-soluble fraction
Cardiovascular function
a. Inhibition of platelet aggregation: adenosine and other related nucleosides
b. Reduction of aconitine, $BaCl_2$ and ouabain-induced arrhythmia: low MW metabolites
Anticancer activities
a. Sterols and their glucosides
b. Low MW metabolites other than cordycepin
c. Modified nucleosides
d. Antitumor function via immunopotentiation and cytokine production: polysaccharides
Immunomodulation
a. Immunopotentiation: polysaccharides
b. Immunosuppression: cyclosporine-like metabolites and others
Hypoglycemic activity in STZ-induced diabetes
Polysaccharides
Erythropoiesis and hemopoiesis
Active ingredient unknown

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energy metabolism in mice. In an animal experiment, mice were given the CS extract (200 mg/kg/day, p.o.) for 3 weeks and *in vivo* ^{31}P NMR spectra of liver were acquired weekly for 3 weeks. A consistent increase in the [ATP]/[Pi] ratio, which represents the high-energy state, was observed in the CS treated mice. No steatosis, necrosis, inflammation, or fibrosis in the liver was observed in the specimens from CS extract-treated animals[4].

Oral administration of the water extracts of CS (WECS) activates *in vivo* Kupffer cell function in rats[5]. After receiving a single i.v. injection of a colloidal carbon solution, the clearance rate from the blood was measured. Test animals were administered daily with WECS (p.o. at 200 mg/kg) for 25 days until the day before the colloidal carbon injection. The half-life of the colloidal carbon in the blood was significantly shorter in the WECS-treated group. The results indicate that stimulation of the Kupffer cell function may partly explain the anti-metastatic action of CS. The stimulating effects of CS, and rat serum containing the same medicine, on IL-1, IFN and TNF produced by Kupffer cells have also been studied in rats[6]. The levels of IL-1, IFN, and TNF, especially those of IL-1 and IFN, produced by cultured rat Kupffer cells are increased by CS, or the drug serum (DS) from animals fed on CS. Treatment of *Paecilomyces sinensis* (i.g. 3g/kg/dx14) increases SOD in the liver of mice[7]. *P. sinensis* inhibits the production of lipid hydroperoxides and increases the amount of SOD in liver homogenates of mice *in vitro*. *P. sinensis* also increases glutathione peroxidase in the liver homogenates of mice.

Disorder of the immune function is one of the important causes of liver cell necrosis, inflammatory cell infiltration, and fibroblastic proliferation. The modulatory effect of cultivated *Cordyceps* hyphae (CH) on immuno-dysfunction of post-hepatitic cirrhosis of patients (n=65) has been reported[8]. The restrained cellular immune functions, including the rate of lymphocyte transformation, the NK cell function, and the $CD8^+$ and $CD4^+$ cells, in the patients' group are lower than those in the healthy group. The $CD8^+$ cell count is positively correlated with the lymphocyte transformation rate and the humoral immune hyperfunction, revealing that the levels of IgG, IgA, ssIgA and CIC of the patients are abnormally high. The C3 is negatively correlated with that of CIC. After CH treatment, the rate of transformation, function of NK cell, $CD8^+$, $CD4^+$ cells and ratio of $CD4^+/CD8^+$ are improved. The levels of IgG, IgA, ssIgA and CIC are reduced, while those of C4 and C3 are increased. In summary, CH treatment modulates the cellular immune function, inhibits the humoral immune hyperfunction, and increases the serum complement level in the patients with post-hepatitic cirrhosis.

The short-term curative effect of cultured mycelia of CS in chronic hepatitis B (HBV) has been demonstrated[9]. Treatment of CS improves the liver function, promotes negative transfer HBsAg, raises plasma albumin, resists high γ-globulin, and adjusts body immuno-competence in HBV patients (n=33). A combination recipe (composed of Semen *Persicae*, *Cordyceps*, Radix *Salviae miltiorrhizae*, *Pollen pini*, and others) in the treatment of 40 posthepatitic cirrhosis patients has been demonstrated[10]. Elevation of lowered plasma branched-chain amino acid to aromatic amino acid ratio has been observed. CS treatment reduces the raised levels of serum laminin and hyaluronic acid. Treated patients also exhibit increased levels of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ratio, NK cells activity and complement C3 and lower levels of IgG and IgM in serum. The combination therapy, which contains CS, is beneficial in the treatment of post-hepatitic cirrhosis. However, the contribution of CS in this combination therapy remains unknown.

Renal Function

Many studies have indicated that CS treatment reduces nephrotoxicity caused by aminoglycoside. The effect of CS on gentamycin-induced nephrotoxicity has been elucidated[11]. CS administration reduces BUN, SCr, sodium excretion, and urinary nephro-aminoglycosidase (NAGase) together with less severity of histopathological changes. CS also promotes an earlier recovery of renal oxygen consumption, inulin clearance, and sodium absorption in isolated perfused kidney of intoxicated rats. Possible mechanisms of CS on aminoglycoside-induced nephrotoxicity include accelerating tubular cell regeneration, protecting the sodium pump activity of tubular cells, attenuating the tubular cell lysosome hyperfunction (stimulated by phagocytosis of aminogly coside), decreasing lipid peroxidation in response to injury, and reducing the Ca^{++} content. CS also reduces aminoglycoside-induced acute renal failure (ARF) in rats[12]. ARF model of rats was induced by i.p. injection of either gentamycin or kanamycin. Simultaneous administration of CS with gentamycin protects the proximal tubular cells from gentamycin-toxicity. After the establishment of kanamycin nephrotoxic ARF, CS treatment causes an earlier recovery from ARF. The possible mechanisms of CS on ARF include protection of tubular cell sodium pump activity, attenuation of tubular cell lysosome overfunction stimulated by phagocytosis of aminoglycoside, and reduction of tubular cell lipid peroxidation in response to toxic injury[12]. The protective effect of CS on aminoglycoside nephrotoxicity in elderly patients has also been observed. Patient groups receiving amikacin sulfate for 6 days were administered with CS or placebo for 7 days. CS-treated group developed less prominent nephrotoxicity as determined by less urinary NAGase and β-microglobulin[13].

The protective effect of CS on cyclosporin A (CsA) nephrotoxicity (CsA-Nx) has also been studied in rats[14]. On the 15th day after receiving CsA, animals developed prominent vacuolation and necrosis in proximal tubular cells and mitochondria swelling. Severe vacuolation (90%) and necrosis appear in proximal tubular cells at different stages of chronic CsA-Nx. Interstitial edema with mild fibrosis also occurs. The epithelial cell areas of tubules and glomeruli are smaller in the CsA group than those in the CS group. These results indicate that CS protects the kidney from CsA-Nx and ameliorates the glomerular and interstitial injuries. Amelioration of cyclosporin nephrotoxicity by CS in kidney-transplanted recipients has also been reported[15]. The effect

of CS on cellular immunity in rats with chronic renal insufficiency has also been demonstrated[16]. Chronic renal failure (CRF) was induced in Wistar rats by 5/6 nephrectomy. CS shows a mitogenic effect on spleen lymphocytes and increases IL-2 production from splenocytes of CRF rats. CS treatment also decreases the levels of BUN and serum creatinine and increases the level of hemoglobin.

CS also stimulates tubular epithelial cell growth[17]. Primary cultured rat tubular epithelium was used to investigate the effect of CS on cellular proliferation and metabolism. Incorporation of ^{3}H-TdR into DNA is increased indicating that CS promotes DNA synthesis and cell proliferation. In association with the beneficial effect to reduce aminoglycoside nephrotoxity *in vivo*, CS may enhance the regeneration of injured tubular cells.

A recent hypothesis suggests that the pathogenesis of immunoglobulin A nephropathy (IgAN) involves the deposition of nephritogenic IgA immune complexes (IgAIC) in the kidney that stimulates resting mesangial cells to release cytokines and growth factors. These cytokines and growth factors cause mesangial cell proliferation and release matrix, chemical mediators that lead to the glomerular injury. In cultured human mesangial cells (HMC) stimulation with IL-1 plus IL-6 causes mesangial cell proliferation and increases production of chemical mediators and superoxide anion. Active fractions and a natural product (CS-H1-A) from CS inhibit the activated human mesangial cell proliferation in this model[18]. The crude methanolic extract from fruiting bodies of CS inhibits HMC activation. The fruiting body extracts were further separated by silica gel column chromatography. A fraction (F-2) inhibits the HMC activation by IL-1 plus IL-6. In IgAN mouse model, R36A (Pneumococcal C-polysaccharide purified from *Streptococcus pneumoniae*) as antigen and anti-R36A IgA MAb form nephritogenic IgA-IC, which induces hematuria and proteinuria in mice with IgA deposition in the mesangial area. Feeding with F-2 (1% w/w in the diet) reduces hematuria and proteinuria together with histopathologic improvement. Treatment with a purified compound (CS-H1-A) from F-2 suppresses the activated HMC and alleviates IgAN with histologic improvement. The study suggests that CS is a potential regimen for the treatment of patients with IgAN[18].

Endocrine and Steroid Hormones

Testosterone-like metabolites and libido-promoting activity have been suspected in CS and in the consumption of CS and CS-containing products for years. However, no direct evidence in the scientific literature is strong enough to link the known CS metabolites to the function. CS stimulates corticosteroid production in animal models. Recently, the action mechanism of CS directly on the adrenal glands or indirectly via the hypothalamus-pituitary axis has been investigated. The effect of a water-soluble extract of CS on steroidogenesis and capsular morphology of lipid droplets in cultured rat adrenocortical cells has been demonstrated[19]. The corticosterone production by adrenal cells, determined by RIA, is increased by CS treatment. The stimulatory effect can be seen 1 hr after CS treatment and maintained for up to 24 hr. Lipid droplets within cells are smaller and fewer. Immunostaining with a MAb, A2, a specific marker for the lipid droplet capsule, demonstrates that detachment of the capsule from the lipid droplet occurs in CS-treated cells. The period required for decapsulation is inversely related to CS in a dose-dependent manner. The CS-induced steroidogenesis is different from that for ACTH, since intracellular cAMP level is not increased in CS-treated cells. Combined treatment with calphostin C, a PKC inhibitor, blocks the effect of CS on steroidogenesis, suggesting that activation of PKC is responsible for the CS-induced steroidogenesis[19].

Cardiovascular Function

Like other medicinal fungi used in Chinese medicine, the mycelia and fruiting bodies of CS are rich in adenosine. Mild hypotensive effect and platelet aggregation inhibition are expected. Vasodilating effect of cultured CS mycelia has been demonstrated in anesthetized dogs[20]. Hot water extract of CS exhibits negative inotropic effect on guinea-pig right atrium *in vitro*[21]. CS inhibits the twitch response of guinea-pig ileum and aggregation of human blood platelet. The activities are ascribed to the combination of adenosine, 5'-AMP, and nucleic acid-related compounds in the extract.

An ethanolic extract (65% ethanol) of CS counteracts the arrhythmia induced by aconitine or $BaCl_2$ in rats[22]. The extract also increases the tolerant dose of ouabain to produce the arrhythmias in guinea pigs. It reduces the heart rate of anesthetic rats, and decreases the contractility of isolated papillary muscle or atria in guinea pigs. However, it has no effect on automatic rhythmicity or functional refractory period of the atria. The ethanolic extract of CS mycelium (CsB-851) also inhibits thrombus formation in abdominal aorta in rabbits[23]. Aortic thrombosis in de-endotheliazed rabbits and ^{51}Cr labeled autologous platelets were used for the evaluation of platelet-vessel wall interaction. CsB-851 treatment reduces the ^{51}Cr labeled platelet number of injured abdominal aorta. It demonstrates that CsB-851 may inhibit thrombus formation at the de-endotheliazed surface of the aorta. CsB-851 inhibits platelet aggregation *in vitro* but has no effect on coagulation *in vivo*. The inhibitory effect of CsB-851 on arterial thrombus formation is related to the inhibition of platelet function.

A double-blind, randomized placebo-control clinical trial has been carried out for the treatment of hyperlipidemia with cultivated *Cordyceps*[24]. No detailed information about the potential ingredients in *Cordyceps* preparation is provided to correlate the clinical observations.

Anticancer Activities

The crude methanolic extract of CS fruiting bodies inhibits the growth of tumor cell lines, namely K562, Vero, Wish, Calu-1, and Raji cells[25]. After further fractionation by using silica gel column chromatography, two fractions

(namely CS-36-39 and CS-48-51) significantly inhibit the growth of these tumor cells. The inhibitory activities are not due to the polysaccharides, which have been eliminated in the extraction and chromatographic separation. These two fractions do not contain cordycepin. This suggests that low-molecular-weight tumor cell growth inhibitors, other than cordycepin and polysaccharides, are present in CS. Antitumor activity of a warm water extract of CS (ECS) against murine tumor cell lines has been observed[26]. Ehrlich ascites carcinoma cells (EAC) allogeneic to ICR mice and Meth A fibrosarcoma (Meth A) syngeneic to BALB/c mice were used as the target tumor cell lines. Animals were inoculated (i.p.) with EAC or Meth A on day 0. ECS was i.p. injected into mice from day 1 to day 4. ECS-treatment increases the survival time of the allogeneic mice inoculated with EAC. More ECS-treated mice survive for 60 days after EAC implantation than control. ECS-treatment also increases the survival time of the syngeneic mice inoculated with Meth A. No cytotoxic effect of ECS was found on either EAC or Meth A *in vitro*. The antitumor effect of ECS in the allogeneic mice is reduced when the mice received whole body X-irradiation (5 Gy) before EAC implantation. This indicates that the antitumor effect of ECS is mediated through its immunomodulating action.

Two antitumor sterols, namely 5α, 8α-epidioxy-24(R)-methylcholesta-6, 22-dien-3β-D-glucopyranoside and 5, 6-epoxy-24(R)-methylcholesta-7, 22-dien-3β-ol have been isolated from the methanolic extract of cultured mycelia of CS[27]. The glycosylated form of ergosterol peroxide at 10 μg/mL inhibits the proliferation of K562, Jurkat, WM-1341, HL-60 and RPMI-8226 tumor cell lines more potently than its aglycone, 5α, 8α-epidioxy-24(R)-methylcholesta-6, 22-dien-3β-ol.

A polysaccharide fraction of CS (PSCS) stimulates the proliferation and differentiation of human leukemic U937 cells[28]. The conditioned medium from PSCS (10 μg/mL)-stimulated blood mononuclear cells (PSCS-MNC-CM) inhibits the proliferation of U937 cells resulting in a growth inhibition rate of 78-83%. PSCS-MNC-CM treatment also induces cells differentiation into mature monocytes/macrophages that express nonspecific esterase activity, CD11b, CD14, and CD68. The differentiated U937 cells maintain functions of phagocytosis and superoxide production. PSCS alone or normal MNC-CM has no such effects. The levels of IFNγ, TNFα, and IL-1 are greatly increased in MNC-CM prepared with PSCS stimulation. An antibody neutralization study indicates that the tumoricidal and differentiating effects of PSCS-MNC-CM are mainly derived from the elevated cytokines, especially IFNγ and TNFα. These cytokines synergistically inhibit cell growth and inducing differentiation. The effects of the ethanolic extract of CS (CS-II) on murine and human *in vitro* natural killer cell (NK) activities, murine *in vivo* NK activity (by ^{125}I clearance assay), and colony formation of B16 melanoma in mouse lungs have been reported[29]. The *in vivo* and *in vitro* NK activities of mice are augmented by i.p. injection of CS-II. The inhibition of NK activity by cyclophosphamide (Cy) is prevented following the administration of CS-II. *In vitro* NK activity of human peripheral blood mononuclear cells (PBMs) is also elevated by preincubation with CS-II. Colony formation of B16 melanoma in mouse lungs is reduced by i.p. pretreatment of animals with CS-II. Potential application of CS-II as an immunopotentiating agent in treating cancer and immuno-deficient patients has been suggested.

Down-regulation of the major histocompatibility complex (MHC) antigens of certain tumors may result in an escape of immune surveillance. CS increases the expression of MHC class II antigens on human hepatoma cells (HA22T/VGH)[30]. In the study, immunostaining with monoclonal antibody (MAb) L243, against the HLA DR region of MHC class II antigens on human hepatoma cells was analyzed by using flow cytofluorimetry. The degree of fluorescence intensity on L243(+) cells was expressed as relative mean fluorescence intensity (RMFI). A methanolic extract of CS (VGH-CS-ME-82) increases MHC class II antigen expression on HA22T/VGH cells with an increase in the percentage of L243(+) cells. VGH-CS-ME-82, either alone or with IFNγ induction, increases the MHC class II antigen expression and makes the host immune surveillance more effective against tumor cells with down-regulated MHC class II antigen expression.

The water extract of CS (WECS) inhibits spontaneous liver metastasis of Lewis lung carcinoma (LLC) and B16 melanoma cells in syngeneic mice (C57BL/6J)[31]. Animals were given an s.c. injection of LLC and B16 cells and sacrificed 20 and 26 days after tumor inoculation, respectively. WECS was administered daily (p.o. 100 mg/kg bw) in the experiment of LLC and in a dose of 100 or 200 mg/kg bw. in the experiment of B16 from one week before tumor inoculation. The relative liver weight of tumor-inoculated mice increases due to tumor metastasis. CS treatment reduces the liver weight in both LLC and B16 experiments indicating that CS has an anti-metastatic activity that is not due to cordycepin. Inhibitory effects of *Cordyceps* on carcinogenesis of the forestomach in mice[32] and antitumor activities of CS and cultured *Cordyceps* mycelia[33] on Lewis lung cancer of mice[34] have also been demonstrated.

In a clinical study, the effect of Jinshuibao capsule (JSBC) (a preparation reported to contain the active principles and pharmacological activity of CS) on the immunologic function of 36 patients with advanced cancer has been reported[35]. JSBC restores cellular immunologic function and improves quality of life, but has no effect on the humoral immunologic function. Detailed information about the cancer type and therapy, other than JSBS, is not described. The report suggests that CS preparation, if properly formulated, may be used as an adjuvant therapy for advanced cancer.

Immunomodulation

Both immunosuppressive and immuno-stimulating functions of CS have been observed. The effects of low-molecular-weight part of CS (methanolic extract and further column fractions) on the lymphoproliferative response, natural

killer (NK) cell activity, and phytohemagglutinin (PHA)-stimulated interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α) production on human mononuclear cells (HMNC) have been elucidated[36]. Two such fractions (CS-36-39 and CS-48-51) inhibited the blastogenesis response, NK cell activity, and IL-2 production of HMNC stimulated by PHA. TNF-α production in HMNC culture is reduced by treatment with CS-36-39 and CS-48-51 indicating that CS contains immuno-suppressive ingredients.

The effects of CS on murine T lymphocyte subsets have been reported[37]. A preparation of CS (Cs-Cr) increases the number of T helper cells and Lyt-1/Lyt-2 (T helper to T suppressor cell) ratio in peripheral blood and spleen. The spleen weight, phagocyte counts, and phagocytic activity are elevated. Cs-Cr protects T helper cells from the immunosuppressive effects of prednisolone acetate and cyclophosphamide. It suggests that Cs-Cr is an immunoregulator of cellular immunity and may be useful in immuno-deficient or immuno-suppressed patients. The immunosuppressive effect of cultured CS on cellular immune response has been further demonstrated *in vitro* and *in vivo*[38]. CS (0.6 to 5 mg/mL) inhibits the following immune reactions of mice in a dose-dependent manner: phagocytic function of peripheral blood leucocytes, mitogenic response of spleen lymphocytes to Con A, and mixed lymphocyte culture and LPS-induced IL-1 release of macrophages. The survival rate of mice spleen lymphocytes cultured with CS is also increased. CS treatment (4 g/kg/d) prolongs the mice skin allograft survival time. The immunosuppressive activity of CS is estimated to be close to that of cyclosporin A (5 mg/kg/d) on skin allograft[39].

CS also has an immunosuppressant effect in the heterotopic heart allograft model in rats[40]. The inhibitory effect of a CS preparation (CS-1) on the immune response responsible for the organ transplant rejection has been studied. CS-1 prolongs heterotopic heart allograft survival in rats with an effect similar to those of cyclosporin A and glucocorticoid. The study suggests that CS can be a promising immunosuppressant in clinical organ transplantation in the future.

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiple organ system involvement. CS improves survival and inhibits anti-ds DNA antibody production in lupus mice (NZB/NZW F1). CS also improves the defective IL-2 production *in vitro* in SLE patients. CS may have great future potential for the management of human SLE[41].

Augmentation of various immune activities of tumor-bearing hosts with an extract of CS (CSE) has been reported[42]. C57BL/6 mice implanted subcutaneously with syngeneic EL-4 lymphoma cells were employed as the host. Oral administration of CSE reduces tumor size and prolongs the host survival time. As judged by plaque-forming cells against T-dependent (sheep erythrocytes) and T-independent (bacterial LPS) antigens, CSE augments the antibody responses. Chemotaxis of peritoneal macrophages is determined within a few days after EL-4 transplantation. Treatment with CSE, at -14, -7, -4, +4, +7 and +10 days after the tumor transplantation, augments the activity by 4-folds. Phagocytic activity of macrophages is decreased in tumor-bearing mice treated with cyclophosphamide 3 and 5 days after tumor transplantation. CSE restores the activity to more than the normal level. CSE also protects against systemic infection by *Salmonella enteritides*. The tumor-bearing mice receiving CSE live longer than control groups. Additional studies support that the pharmacological actions of CS on murine immune organs, such as CS action after irradiation with ^{60}Co gamma-ray, are mainly mediated through the host immune system[42-45]. In summary, the effects of natural CS and its cultured mycelia on murine immuno-organs, the function of the mononuclear macrophage system, and cellular immunity have been demonstrated in many studies[46-48].

Several clinical studies have been carried out to investigate the potential of CS on declined immune function. The effects of CS on peripheral NK cells from healthy persons and leukemia patients have been studied[49]. CS treatment augments NK cell activity and increases CD16 expression in lymphocytes and the binding capacity to K562 cells. CS as an adjunct therapy in the treatment of leukemia has been suggested[49]. The modulating effect of CS on T-lymphocyte subsets in chronic renal failure also deserves attention[50]. In a clinical study, synchronous measurement of renal function and T-cell subsets were taken in patients of chronic renal failure (CRF) (n=51). Patients (n=28) taking CS (3-5 g/d) were considered as a study group. A significant decrease of OKT3, OKT4, OKT4/OKT8 was found in CRF indicating that cellular immune function is decreased in CRF. CS treatment improves renal function and increases the OKT4 and OKT4/OKT8 ratio[50]. The study indicates that CS may improve renal function and simultaneously enhance the cellular immune function in CRF.

Polysaccharides and Their Biological Activities

Fungal polysaccharides are commonly recovered from the fruiting bodies and cultured mycelia by aqueous extraction at elevated temperature, followed by ethanol precipitation. Many polysaccharides with antitumor, immunomodulatory, and hypoglycemic activities have been isolated from Chinese medicinal fungi and related species, including *Ganoderma*, *Cordyceps*, *Auricularia*, and *Poria*[51]. The isolation of hypoglycemic polysaccharides from the cultural mycelium of CS has been reported[52]. Intraperitoneal (i.p.) injection of crude polysaccharides, obtained from a hot-water extract and alkaline extracts of CS mycelium, shows hypoglycemic activities in normal and streptozotocin (STZ)-induced diabetic mice but slightly reduces the plasma glucose in normal mice by oral administration. Oral administration of (50 mg/kg) of CS-OHEP, a crude polysaccharide preparation obtained from 5% sodium hydroxide extraction, reduces plasma glucose without affecting plasma insulin level in normal mice. A neutral polysaccharide (CS-F30; MW about 45 kDa) exhibited higher hypoglycemic activity than CS-OHEP by i.p. injection. CS-F30 is composed of galactose, glucose, and mannose in molar percent of 62:28:10. CS-F30 exhibits a hypoglycemic activity in genet-

ic diabetic mice after i.p. administration. It also quickly reduces plasma glucose in normal and STZ-induced diabetic mice after i.v. administration. Administration of CS-F30 to normal mice increases hepatic glucokinase, hexokinase and glucose-6-phosphate dehydrogenase activities and reduces hepatic glycogen content. CS-F30 also lowers the plasma triacylglycerol and cholesterol levels in mice[53].

Pharmacology and structural information of polysaccharides derived from species of genus *Cordyceps* other than *C. sinensis* deserve great attention. Two bioactive galactomannans (CI-P and CI-A), isolated from the insect body portion of Chan hua (*Cordyceps cicadae*), have been studied in detail[54]. CI-P having low affinity for Con A exhibits carbon-clearance activity in mice. CI-P and CI-A have little antitumor activity against sarcoma 180 in mice but have hypoglycemic activities in normal mice.

A water-insoluble, alkali-soluble extracellular glucan (CO-1) (average MW about 632 kDa) has been isolated from *Cordyceps ophioglossoides*[55]. ^{1}H- and ^{13}C-NMR and IR spectral data indicate that the glucosidic linkages in CO-1 are beta. CO-1 is composed of a backbone of (1-3)-linked β-D-glucopyranosyl residues with a β-D-glucopyranosyl group attached to O-6 of every second D-glucopyranosyl residue of the backbone. CO-1 inhibits the growth of Sarcoma 180 solid-type tumor[56].

Gal β-(1-3) GalNAc-Ser/Thr occurs in the linkage region of the polygalactosamine containing glycoprotein from *C. ophioglossoides*[57]. Deamination by nitrous acid liberates the N-acetyl galactosamine containing glycoproteins from galactosminoglycan (CO-N) which has been isolated from *C. ophioglossoides* culture. Mild alkaline borohydride degradation of the purified glycoprotein releases oligosaccharide alditols. The smallest oligosaccharide alditol has been characterized to be Gal β-(1-3) GalNAcol. It indicates that the polygalactosamine part is attached to the protein part via Gal beta (1-3) GalNAc-Ser/Thr as the linkage.

Antitumor activity of a protein-bound polysaccharide fraction (SN-C) from *C. ophioglossoides* has been demonstrated in mice[58]. In transplanted allogeneic and syngeneic murine tumor models, i.p. administration of SN-C suppresses the tumor growth of sarcoma-180. SN-C also prolongs the life span of ICR mice inoculated (i.p.) with Ehrlich carcinoma, and C3H/He mice inoculated with a syngeneic tumor (X-5563). SN-C has no effect on delayed-type hypersensitivity (DTH) in normal mice, but can restore the depressed capacity to raise DTH in tumor-bearing mice indicating that SN-C exerts direct and host-mediated antitumor effects[59]. The galactosaminoglycan moiety (CO-N) has been obtained from an antitumor polysaccharide fraction (SN-C) produced by *C. ophioglossoides*[60]. After sonication of SN-C, CO-N can be isolated by precipitation with 10% ammonium hydroxide. When given i.p. to mice, CO-N inhibits the proliferation of sarcoma 180 cells inoculated into the peritoneal cavity and has a life-prolonging effect against ascitic tumors such as Ehrlich carcinoma and IMC carcinoma. CO-N inhibits solid Ehrlich carcinoma when given intratumorally and also inhibits the growth of a syngeneic solid tumor (MM46 mammary carcinoma) upon iv administration. CO-N has a cytocidal effect against cultured IMC and P388D1 cells. CO-N exhibits a broad MW distribution with an average MW of 33 kDa[61]. The low-MW fraction (MW<6600 Da) has a weak antitumor activity. Depolymerized CO-N (ca. 5500 Da), obtained by extensive ultrasonication of CO-N, retains the antitumor activity of CO-N against Ehrlich ascitic carcinoma and MM46 solid mammary carcinoma.

Erythropoiesis and Hemopoiesis

CS stimulates erythropoiesis in mouse bone marrow[62]. A preparation of CS (CS-Cr) stimulates proliferation of erythroid progenitor cells (CFU-E and BFU-E) in LACA mouse marrow *in vivo* and *in vitro*. The numbers of CFU-E and BFU-E increase after a 5-day treatment with CS-Cr (100, 150 and 200 mg/kg). Higher doses (> 150 mg/kg) result in a reduction of the peak of CFU-E and BFU-E. Ara-C increases in the percentage of CFU-E and BFU-E cells in S-phase after CS-Cr treatment. Pretreatment of mice with CS-Cr protects CFU-E and BFU-E against harringtonine (a cytotoxic agent). Addition of CS-Cr (150-200 μg/mL) to culture system stimulates the generation of CFU-E and BFU-E *in vitro*. The stimulatory action of CS-Cr on fibroblast colony-forming units (CFU-F) proliferation has been observed *in vivo* and *in vitro*[62]. Platelet hemopoiesis and ultrastructure changes in mice treated with natural CS and cultured mycelia have also been observed[63].

Natural Product Chemistry and Pharmacological Functions

Many natural products have been identified from the fruiting bodies and cultured mycelium of *Cordyceps* and related species. The chemical constituents[64] including sterols and their glucosides, nucleosides, polysaccharides in CS have been reported[25, 27, 65]. Reversed-phase HPLC is the most common tool used for the comparison of chemical constituents of CS and related species, such as *Cordyceps barnesii*[66] and *Cordyceps mililaris*[67, 68]. Ophiocordin, originally isolated from *Cordyceps ophioglossoides*[69], has been found to be identical to the potent protein kinase C (PKC) inhibitor balanol from the fungus *Verticillium balanoides*[70]. Production of cordycepin (3'-deoxyadenosine) in *Cordyceps militaris* has been reported since 1964[71, 72]. The metabolic fate of adenosine and cordycepin in cordycepin biosynthesis has been conducted in *C. militaris*[73]. However, the content of cordycepin in CS is either very low or not detectable[74].

CONCLUSION

Many studies *in vitro* and *in vivo* support that *Cordyceps sinensis* has diverse biological activities and pharmacological potential (Table 1). The effects in renal and hepatic function and immunomodulation-related antitumor activities are most promising and deserve great attention. Although the origin and preparation of *Cordyceps* are not always clearly

addressed in publications, most studies use water-soluble, polysaccharide-rich fractions or alcohol extracts. Many studies use fruiting bodies as the part of investigation. However, recently an increasing number of studies have used cultured mycelia. It is difficult to determine if the same bioactive ingredients exist in fruiting bodies and cultured mycelia in these pharmacological studies. Future study of this medicinal fungus greatly depends on the use of chemically defined and pharmacology-proven fungal materials. Fermented mycelia, which can be constantly produced in a large scale, are a better source of this herbal medicine. More mechanism-based, disease-oriented pharmacological studies are required to ensure clinical application. Furthermore, adjuvant therapy of *Cordyceps sinensis* in immune function disturbances, cancer, and renal failure is a possibility.

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中國藥用真菌冬蟲夏草及相關真菌的藥理功能

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摘　要

冬蟲夏草是一種使用於傳統中國醫藥上的蟲生真菌，具有廣泛的生物活性，並特別表現在腎臟、肝臟、心血管、免疫系統方面的藥理功能。蟲草菌的藥理作用主要是因為冬蟲夏草及相關真菌可產生具有生物活性的多醣體、修飾型核啟及環胞素型的代謝物所致。冬蟲夏草的藥理作用亦因而以在腎與肝功能及免疫調節上的表現最值得關注。先前的研究多採用子實體為藥材，最近的藥理作用研究報告中，採用培養菌絲體為對象者已逐漸增多。然而，目前並無法依文獻資料判斷子實體與菌絲是否均產生相同有效成份而導致其藥理效果。未來宜有更多疾病導向且以作用機轉為基礎的藥理學研究，以強化冬蟲夏草用於特定疾病的臨床基礎。目前資料顯示，若能再於雙盲、隨機且安慰劑控制組之臨床試驗顯示有效，則冬蟲夏草最可能使用於免疫功能變異、癌症、腎功能衰敗的輔助治療方面。

關鍵詞：冬蟲夏草，抗癌活性，肝功能，腎功能，免疫調節，多醣體，修飾型核啟