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Review Article

Pharmacological actions of *Cordyceps*, a prized folk medicine

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Abstract

Cordyceps species, including *C. sinensis, C. militaris, C. pruinosa* and *C. ophioglossoides*, are prized traditional medicinal materials. The aim of this article is to review the chemical constituents and pharmacological actions of *Cordyceps* species. The chemical constituents include cordycepin (3′-deoxyadenosine) and its derivatives, ergosterol, polysaccharides, a glycoprotein and peptides containing α-aminoisobutyric acid. They include anti-tumour, anti-metastatic, immunomodulatory, antioxidant, anti-inflammatory, insecticidal, antimicrobial, hypolipidaemic, hypoglycaemic, anti-ageing, neuroprotective and renoprotective effects. Polysaccharide accounts for the anti-inflammatory, antioxidant, anti-tumour, anti-metastatic, immunomodulatory, hypoglycaemic, steroidogenic and hypolipidaemic effects. Cordycepin contributes to the anti-tumour, insecticidal and antibacterial activity. Ergosterol exhibits anti-tumour and immunomodulatory activity. A DNase has been characterized.

Introduction

Cordyceps is a renowned traditional Chinese medicinal material comprised of dried fungus, belonging to the genus *Cordyceps*, growing on the caterpillar. It is an obligatory parasite that grows on insects, or insect larvae. It has been used as a tonic for the weak. A voluminous amount of information about the diversity of biological actions of various *Cordyceps* species is available. There has been a growing commercial interest in the medicinal uses of *Cordyceps*. Thus it is timely to summarize the information and present it in a review.

Chemical constituents

A variety of compounds have been purified and their structures elucidated. Cordycepin (3′-deoxyadenosine), 3′-amino-3′-deoxyadenosine, homocitrullyl aminoadenosine, adenine, cordycepic acid and D-mannitol have been reported from *Cordyceps* species (Cunningham et al 1950; Chatterjee et al 1957; Kredich & Guarino 1961; Guarino & Kredich 1963; Kaczka et al 1964; Liu et al 1989). Li et al (2001a, b) found that cultured *C. sinensis* mycelia have a much higher content of nucleosides than natural *C. sinensis*. Guo et al (1998) described an HPLC method for quantitative determination of adenosine and 3′-deoxyadenosine. Li et al (1999) determined adenosine in fermented products of *Cordyceps* by reversed-phase HPLC.

Ergosterol in *C. sinensis* can be determined by HPLC (Li & Li 1991; Li et al 2004a). Boros et al (1994) reported that ophiocordin, an antifungal antibiotic from *C. ophioglossoides* (Kneifel et al 1977) and balanol from *Verticillium balanoides* are structurally identical. Bioxanthracenes were isolated from *C. pseudomilitaris* (Isaka et al 2001a; Jaturapat et al 2001). Four exopolysaccharides with different molecular masses ranging from 50 kDa to 2260 kDa were reported from *C. militaris* by Kim et al (2003b, c).

Huang et al (2003) described a simple and rapid isocratic LC/MS coupled with electrospray ionization method for simultaneous separation and determination of adenosine, adenine, hypoxanthine and cordycepin in *C. sinensis*. Sun et al (2003) separated the nucleosides in natural and cultured *C. kyushuensis* by high-performance capillary zone electrophoresis, and found differences between natural and cultured fungi and between different parts of the fungus. Li et al (2004a) simultaneously determined ergosterol and nucleosides, and their bases, from natural and cultured *Cordyceps*. The water-soluble constituents of natural *Cordyceps* can be distinguished, by fingerprinting using capillary electrophoresis, from those of cultured *Cordyceps* (Li et al 2004b). Huang et al (2004b)

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described a method for concurrent determination of adenosine and cordycepin in *C. sinensis* and *C. militaris*. Gong et al (2004) reported a method for simultaneous determination of adenine, adenosine, guanosine, uracil, uridine and inosine in *Cordyceps* by capillary electrophoresis.

Yu et al (2004a, b) isolated four polysaccharides from *C. militaris*. Ten-membered macrolides, cepharosporolides C, E and F, cordycepin, pyridine-2, 6-dicarboxylic acid and 2-carboxymethyl-4-(3′-hydroxybutyl) furan were reported from *C. militaris* by Rukachaisirikul et al (2004). Krasnoff et al (2005) reported cicadapeptins I and II (peptides containing α-aminoisobutyric acid) and myriocin (a fungicide) from *C. heteropoda*.

A glycoprotein with *N*-acetylgalactosamine was isolated from *C. ophioglossoides* (Kawaguchi et al 1986).

Anti-inflammatory activity

Treatment with water extract of *C. sinensis* (0.1 or 0.2 g) brings about a down-regulation of inflammation-related genes in the rat kidney following ischaemia/reperfusion (Shahed et al. 2001). It improves lung function in sensitized guinea pigs and airway inflammation in sensitized rats, suggesting that it could be used in the prevention and treatment of asthma (Lin et al 2001). The methanol extract of *C. pruinosa* inhibits the gene expression of interleukin-1β, tumour necrosis factor-α, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2, and suppresses nuclear transcription factor NF-κ B activation in the lipopolysaccharide (LPS)-stimulated mouse macrophage cell line RAW 264.7. The data indicate that the methanolic extract of *C. pruinosa* is probably useful for the treatment of endotoxin shock or sepsis (Kim et al 2003a). A polysaccharide from the aqueous extract of cultured *C. militaris* demonstrates anti-inflammatory activity (Yu et al 2004a). The 70% ethanolic extracts of cultured fruiting bodies and mycelia of *C. militaris* applied topically (0.5 mg/ear) exhibit anti-inflammatory activity (about 50% inhibition of ear plug weight) in the croton oil-induced ear oedema test in mice. Nitric oxide production and iNOS gene expression in LPS-stimulated RAW 264.7 cells are suppressed (Won & Park 2005).

Antioxidant, neuroprotective and anti-ageing activity

Jinshuibao capsule, a preparation of *C. sinensis*, when tested in senile patients, increases the depressed superoxide dismutase activity and reduces the elevated malondialdehyde (MDA) level caused by ageing. In animal experiments the preparation enhances the repair of damaged DNA (Zhang et al 1997).

Aqueous and ethanolic extracts of *C. sinensis* inhibit MDA generation via hydroxyl radicals induced by the peroxynitrite generator SIN-1, and suppress the oxidation of low-density lipoprotein (LDL) and macrophage accumulation of esterified cholesterol (Yamaguchi et al 2000a, b). Tsai et al (2001) demonstrated the hydroxyl radical scavenging activity of an aqueous extract of *C. sinensis*. Shen & Chen (2001) showed that *C. militaris* extract reduces lipid peroxidation induced by inhalation of n-hexane in rats. Li et al (2001a) noted that water extracts, as well as a partially purified polysaccharide fraction, of cultured *C. sinensis* mycelia manifest antioxidant activity in the xanthine oxidase, haemolysis and lipid peroxidation assay systems. Subsequently, Li et al (2002) showed that the fruiting body part and the caterpillar part of *C. sinensis* are similar in chemical composition and antioxidant activity because the mycelia have invaded the caterpillar. Cho et al (2003) reported that *Cordyceps* extract possesses 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity. Wang et al (2005) also noted that the ethanol extract of *C. sinensis* exhibits free radical scavenging activity. Fraction R, derived from the ethanolic extract, at a concentration of 2 mg mL^{-1}, scavenged 93% of 1,1-diphenyl-2-picrylhydrazyl free radicals. Its IC50 value on colorectal tumour cells was 2 μg mL^{-1}.

Paecilomyces japonica, a new type of *Cordyceps* species, contains a protein-bound polysaccharide that inhibits lipid peroxidation and increases the activity of antioxidant enzymes, such as catalase and superoxide dismutase, in the liver (Shin et al 2001). Liu et al (1991) showed that *P. sinensis* inhibits lipid peroxidation but increases the amount of glutathione peroxidase and superoxide dismutase in mouse liver.

A 210-kDa polysaccharide from *C. sinensis* mycelia protects phaeochromocytoma PC12 cells against H_2O_2-induced injury (Li et al 2003). Methanolic extracts of *C. ophioglossoides* mycelia prevent β-amyloid (25-35)-induced cell death in SK-N-SH neuronal cells and memory deficits in rats (Jin et al 2004).

Chen & Li (1993) compiled a list of anti-ageing traditional Chinese medicinal materials, one of which was *Cordyceps*. Treatment of D-galactose-induced aged mice with *C. sinensis* extract results in an improvement in learning ability and memory, increase in superoxide dismutase activity in erythrocytes, liver and brain, increase in catalase and glutathione peroxidase activity in blood, reductions in malondialdehyde levels in brain and liver and reduction in monoamine oxidase activity in brain (Wang et al 2004).

Anti-tumour, anti-proliferative and anti-metastatic activity

Yamada et al (1984) reported that a water-insoluble extracellular glucan (CD-1) isolated from the culture filtrate of *C. ophioglossoides* potently suppresses the growth of sarcoma 180 solid-type tumour. The glucan has 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. Lin (1984) described the suppressive action of *Cordyceps* on carcinogenesis in the murine forestomach. Ohmori et al (1986) isolated a protein-bound polysaccharide fraction (SN-C) from *C ophioglossoides*, which lengthened the life span of mice bearing Ehrlich carcinoma and mice bearing a syngeneic tumour, X-5563. Ohmori et al (1989a, b) isolated from SN-C a galactosaminoglycan (CO-N) that inhibits the proliferation of sarcoma 180 cells and the growth of a syngeneic solid tumor (MM46 mammary carcinoma) in-vivo and exhibits cytotoxicity against IMC and P388D1 cells in-vitro. CO-N

has a broad molecular weight distribution with an average of 33 kDa and anti-tumour activity enriched in the fraction with a higher molecular weight.

A water extract of *C. sinensis* increases the median survival time of ICR mice inoculated with allogeneic Ehrlich ascites carcinoma cells and BALB/c mice inoculated with syngeneic Meth A fibrosarcoma cells (Yoshida et al 1989). Xu et al (1992) found that an ethanolic extract of *C. sinensis* inhibits B16 melanoma colony formation in murine lungs. Kuo et al (1994) reported that substances other than cordycepin and polysaccharides are present in the methanolic extract of *C. sinensis*. These substances inhibit the growth of Calu-1, K562, Raji, Vero and Wish tumour cells.

Chen et al (1997) observed that the conditioned medium from blood mononuclear cells stimulated with the polysaccharide fraction from *C. sinensis* inhibits the proliferation of human leukaemic U937 cells, and induces about half of the cells to differentiate into mature monocytes/macrophages expressing nonspecific esterase activity and CD116, CD14 and CD68 surface antigens. The antiproliferative and differentiating effects were shown to be caused by an elevated production of cytokines, in particular tumour necrosis factor-α and interferon-γ.

The glycosylated form of ergosterol peroxide from *C. sinensis* is more potent than its aglycone, 5α-8α-epidioxy-24(*R*)-methylcholesta-6,22-dien-3β-ol, in inhibiting the proliferation of HL-60, Jarkat, K562, RPMI-8226 and WM-1341 tumour cells (Bok et al 1999).

C. militaris inhibits the growth and metastasis of Lewis lung cancer cells implanted in mice, and inhibits the growth of sarcoma S180 cells implanted in mice and lengthens the survival period of the mice (Liu et al 1997). *C. militaris* extract inhibits the growth of human umbilical vein endothelial HUVEC cells and HT 1080 cells. It down-regulates, in a dose-dependent and a time-dependent manner, bFGF gene expression in HUVEC cells and MMP-9 gene expression in HT 1080 cells. The growth of B16-F10 melanoma cells in mice is suppressed. At a dose of 100 μg mL^{-1} of the extract, a reduction of 6% and 14.9% of MMP-9 gene expression is detected after 3 h and 6 h of incubation, respectively. At a dose of 200 μg mL^{-1}, a decrease of 22.9% and 32.8% MMP-9 gene expression is observed. In addition, *C. militaris* extract manifests anti-angiogenic activity (Yoo et al 2004). The exopolysaccharide fraction of *C. sinensis* inhibits metastasis of B16 melanoma cells to the lungs and the liver and at the same time down-regulates the levels of Bcl-2 protein in these organs (Zhang et al 2004b). Cordycepin inhibits the growth of B16 melanoma cells inoculated subcutaneously into right murine footpads (Yoshikawa et al 2004). The ethanol extract of the fruiting bodies of *P. japonica* reduces the tumour weight and volume and lengthens the life span of mice inoculated with sarcoma 180 cells (Shin et al 2003).

The ethyl acetate extract of *C. sinensis* mycelia induces apoptosis in human pre-myelocytic leukaemia HL60 cells, as demonstrated by DNA fragmentation and chromatin condensation, caspase activation and specific cleavage of poly ADP-ribose polymerase. Cell proliferation is inhibited (Zhang et al 2004a). Apoptosis is detectable 6–8 h after treatment with the extract at a dosage of 200 μg mL^{-1}. After treatment for 2 days the ED50 is found to be 25 μg mL^{-1}.

The water extract of *C. sinensis* inhibits spontaneous liver metastasis of Lewis lung carcinoma cells and B16 melanoma cells in syngeneic mice. It demonstrates potent cytotoxicity against these tumour cells, while cordycepin is devoid of cytotoxicity, suggesting that the anti-metastatic activity is not attributed to cordycepin (Nakamura et al 1999a). Co-administration of the water extract and methotrexate prolongs the survival period of mice inoculated with B16 melanoma cells compared with administration of the water extract alone and administration of methotrexate alone (Nakamura et al 2003). Apoptosis of melanoma cells is observed 48 h after treatment with the water extract at a dose of 100 μg mL^{-1}. The enhanced function of Kupffer cells is partly involved in the anti-metastatic function of the water extract (Nakamura et al 1999b). At a concentration of 12.5 μM, HI-A isolated from *C. sinensis* inhibits proliferation of human mesangial cells and promotes apoptosis, suppressing Bcl-2 and Bcl-XL phosphorylation (Yang et al 2003).

Immunomodulatory activity

Zhang (1985) reported the macrophage-stimulating activity of natural *C. sinensis* and its cultured mycelia. *C. sinensis* extract enhances the antibody response as judged by plaque-forming cells against T-dependent and T-independent antigens, like ovine red blood cells and bacterial lipopolysaccharide, respectively. The extract also restored the phagocytic activity of macrophages in tumour-bearing mice that received cyclophosphamide several days after tumour transplantation, and lengthened the survival period (Yamaguchi et al 1990).

Zhang & Xia (1990) demonstrated that *C. sinensis* acts as an immunosuppressant in the heterotropic heart allograft model in rats and prolongs the survival period. Zhu & Hu (1990) found that *C. sinensis* prolongs the mouse skin allograft survival time. *C. sinensis* increases the number of T helper cells and Lyt-1/Lyt-2 (T helper cells to T suppressor cells) both in peripheral blood and spleen (Chen et al 1991).

C. sinensis exerts a mitogenic action on splenic lymphocytes and augments interleukin-2 from spleen cells of rats with chronic renal failure (Cheng 1992). Natural killer cell activity is enhanced, and the reduction of this activity brought about by cyclophosphamide is prevented (Xu et al 1992). *C. sinensis* treatment of patients with post-hepatic cirrhosis results in an enhancement of natural killer cell function, an increased number of CD4+ and CD8+ cells, an improved ratio of CD4+/CD8+, and reduction in IgA and IgG levels (Zhu & Liu 1992). *C. sinensis* treatment of patients with chronic hepatitis B results in increases in CD4 and CD4/CD8 ratio, and reductions in hyaluronic acid and procollagen type III. The data indicate the usefulness of *C. sinensis* to adjust the level of T lymphocyte subsets and to treat hepatic fibrosis in patients with chronic hepatitis B (Gong et al 2000). *C. sinensis* increases activity of peripheral natural killer cell activity from healthy subjects and leukaemia patients (Liu et al 1992). *C. sinensis* improves renal function and augments cellular immune function in patients with chronic renal failure (Guan et al 1992). Zhou & Lin (1995) reported that Jinshuibao, a preparation of *C. sinensis*, restores cellular immune function and improves the quality

of life in patients with advanced cancer without affecting humoral immune function. Two of the fifteen column fractions derived from the methanol extract of *C. sinensis* fruiting bodies inhibit the blastogenesis response, natural killer cell activity, interleukin-2 production and tumour necrosis factor-α production in phytohaemagglutinin-stimulated human mononuclear cells (Kuo et al 1996). *C. sinensis* elevates the levels of interferon, interleukin-1 and tumour necrosis factor produced by cultured rat Kupffer cells (Liu et al 1996a).

The methanolic extract of *C. sinensis* inhibits proliferation of cells in bronchoalveolar lavage fluid (BALF), and reduces production of interleukin-6, -8 and -10 and tumour necrosis factor-α in LPS-activated BALF cell cultures (Kuo et al 2001). The hot-water extract of *C. sinensis* mycelia ($1\,g\,kg^{-1}$ daily for 7 days) modulates interleukin-6 production by activation of macrophages and augments the secretion of haematopoietic growth factors (Koh et al 2002).

Aqueous methanolic (50%) extracts of the asocarp part of *C. cicadae* stimulate proliferation of phytohaemagglutinin-induced proliferation of human mononuclear cells (HMNC) with an EC50 of $138 \pm 4.6\,\mu g\,mL^{-1}$. In contrast, methanolic (100%) extracts of the insect-body part inhibit proliferation of HMNC with an IC50 of $32.5 \pm 5.2\,\mu g\,mL^{-1}$. The production of interleukin-2 and interferon-γ is stimulated by the aqueous methanolic extracts and inhibited by the methanolic extracts (Weng et al 2002). *C. sinensis* treatment of patients with condyloma acuminata brings about an increase in interleukin-2 and a decrease in interleukin-10, indicating a recovery in the balance of Th1/Th2 cytokines. The recurrence of condyloma acuminata is also diminished (Gao et al 2000). The hot-water extract of *C. scarabaecola* stromata exhibits potent intestinal immune-system-modulating activity, while the methanol-soluble fraction manifests intermediate activity (Yu et al 2003).

Ergosterol peroxide isolated from *C. cicadae* inhibits phytohaemagglutinin-induced T cell proliferation, and arrests the progression of activated T cells from G1 to S phase of the cell cycle. Early gene transcripts, in particular those of cyclin E, interferon-γ, interleukin-2 and interleukin-4, are suppressed (Kuo et al 2003). The exopolysaccharide fraction of cultivated *C. sinensis* stimulates the peritoneal macrophages to take up neutral red and splenic lymphocytes to proliferate (Zhang et al 2004b). *P. japonica* exhibits immunostimulating activity. Its ethanolic extract stimulates phagocytosis and macrophage acid phosphatase activity (Shin et al 2001, 2003).

C. ophioglossoides galactosaminoglycan reacts with sera from patients with some collagen diseases and its use as an index of serological activity is thus of diagnostic value (Ikeda et al 1993).

Effect on erythropoiesis and apoptosis of cells

C. sinensis crystal (100, 150 and $200\,mg\,kg^{-1}$) stimulates proliferation of erythroid progenitor cells in mouse bone marrow (Li et al 1993).

C. sinensis extract down-regulates apoptotic genes in the rat kidney following ischaemia/reperfusion (Shahed et al 2001). The compound HI-A from *C. sinensis* inhibits the proliferation of human mesangial cells and promotes apoptosis by suppressing tyrosine phosphorylation of Bcl-2 and Bcl-XL (Yang et al 2003).

Buenz et al (2004) reported that aqueous, organic and alcoholic *C. sinensis* extracts are not able to protect T cells from apoptosis induced by Fas or H_2O_2.

Effect on insulin secretion and hypoglycaemic activity

The galactomannans CI-A and CI-P isolated from the insect portion of *C. cicadae* demonstrate potent hypoglycaemic activity in normal mice (Kiho et al 1990). A crude polysaccharide (designated as CS-OHFP) and a neutral polysaccharide (designated as CS-F30) exert hypoglycaemic activity in normal mice. CS-F30, which possesses a molecular mass of 45 kDa and is composed of galactose, glucose and mannose in a molar ratio of 62:28:10, does not affect the circulating insulin level in normal mice (Kiho et al 1993). CS-F30 also lowers the plasma glucose level in streptozotocin-induced diabetic mice and in genetically diabetic mice (Kiho et al 1996). Another polysaccharide (designated as CS-F10) from a hot-water extract of *C. sinensis* mycelia also lowers the plasma glucose level in normal, adrenaline-induced hyperglycaemic and streptozotocin-induced diabetic mice. It exhibits a molecular mass of 15 kDa and is composed of galactose, glucose and mannose in a molar ratio of 43:33:24 (Kiho et al 1999).

CordyMax Cs-4, a mycelial fermentation product of *C. sinensis*, lowers fasting plasma levels of glucose and insulin, improves oral glucose tolerance and increases the glucose-insulin index, which measures insulin sensitivity, in rats (Zhao et al 2002). The product increases whole-body insulin sensitivity in rats (Balon et al 2002).

C. sinensis increases the basal plasma insulin level (Zhang et al 2003) and inhibits hepatic fibrogenesis (Zhang et al 2004c) in rats with CCl_4-induced liver fibrosis. The fruiting body portion (1 g daily for 4 weeks), but not the carcass portion, of *Cordyceps* (1 g daily for 4 weeks) reduces weight loss, polydipsia and hyperglycaemia in streptozotocin-induced diabetic rats (Lo et al 2004). The water extract of *C. militaris* (0.5 g/kg diet) reduces the fasting serum glucose level and enhances glucose utilization in skeletal muscles in rats (Choi et al 2004).

Effect on the kidneys

C. sinensis increases DNA synthesis in primary cultured rat tubular epithelial cells (Tian et al 1991). *C. sinensis* protects proximal tubular cells from the toxic effects of gentamicin. The possible mechanisms include protection of sodium pump activity of the tubular cells, reducing lipid peroxidation in tubular cells and attenuating lysosomal over-activity in tubular cells due to phagocytosis of gentamicin (Zhen et al 1992; Li et al 1996). *C. sinensis* also protects the rat kidney from ciclosporin-induced nephrotoxicity and ameliorates glomerular and interstitial damage (Zhao & Li 1993). Similar findings in kidney-transplant recipients were obtained by Xu et al (1995). Bao et al (1994) reported

that *C. sinensis* protects old patients from amikacin sulfate toxicity as demonstrated by decreases in urinary nephro-aminoglycosidase and β-microglobulin.

HI-A from *C. sinensis* alleviates immunoglobulin A nephropathy (Berger's disease) with histological and clinical improvement (Lin et al 1999).

C. militaris and *C. sinensis* inhibit LDL-induced proliferation of cultured human glomerular mesangial cells, which are involved in the development of glomerulosclerosis (Zhao-Long et al 2000).

Bailing capsule, a dry powder preparation of *C. sinensis* mycelia, prevents rejection of renal transplants, protects renal and hepatic function, stimulates haematopoietic function, improves hypoproteinaemia and hyperlipidaemia and reduces the incidence of infections (Sun et al 2004).

Effect on gonadal and adrenal steroidogenesis

C. sinensis mycelia induce human granulosa-lutein cells to produce 17β-estradiol by upregulating expression of steroidogenic acute regulatory protein (StAR) and aromatase (Huang et al 2004a). Steroidogenesis in MA-10 mouse Leydig tumour cells is also stimulated by *C. sinensis* mycelia (Huang et al 2001a) without involvement of StAR (Huang et al 2000). Two fractions of *C. sinensis* mycelia, namely, a water-soluble polysaccharide fraction F1 and a poorly water-soluble polysaccharide, and a protein fraction, F3, stimulate steroidogenesis (Huang et al 2001b). However, *C. sinensis* mycelia inhibit testosterone production stimulated by human chorionic gonadotropin or dibutyryl cyclic AMP, indicating that its effect on the signal transduction pathway for steroidogenesis lies after the production of cyclic AMP. Protein synthesis is required for the action of *C. sinensis* since its ac-tion is blocked by cycloheximide (Huang et al 2001b). Subsequently, Hsu et al (2003b) demonstrated that *C. sinensis* inhibits the activity of cytochrome P450 scc to reduce human chorionic gonadotropin-stimulated testosterone production in mouse Leydig cells. Hsu et al (2003a) showed that *C. sinensis* and fractions derived from it are capable of stimulating testosterone production both in-vitro and in-vivo. The steroidogenic activity is observed in-vivo in both immature and mature male mice after 7 days of treatment at a dose of 0.02 or 0.2 mg g^{-1} (Huang et al 2004c).

Chen et al (2005) found that *C. sinensis* acts on both protein kinase A and protein kinase C pathways to stimulate steroidogenesis in MA-10 mouse Leydig tumour cells. Inhibitors of protein kinase A, protein kinase C and phospholipase C and calmodulin antagonists reduce Leydig cell steroidogenesis induced by *C. sinensis*. A water-soluble extract of *C. sinensis* increases corticosterone output by cultured rat adrenocortical cells without increasing the intracellular cAMP level. The steroidogenic effect of *C. sinensis* is abolished by the protein kinase C inhibitor calphostin C, indicating that its action may involve stimulation of protein kinase C (Wang et al 1998).

Effect on the liver

Zhu & Liu (1992) found that cultivated *Cordyceps* mycelia inhibit humoral immune hyperfunction and increase the serum complement level in patients with post-hepatic cirrhosis, and improve liver function.

Manabe et al (1996, 2000) found that *C. sinensis* mycelial extract (200 mg kg^{-1} daily orally) increases hepatic energy metabolism, as demonstrated by liver ATP:Pi value, in diet-induced hypoferric anaemic mice by increasing hepatic blood flow. *C. sinensis* stimulates mitochondrial electron transport and ATP production (Siu et al 2004). Dai et al (2001) found that CordyMax Cs-4 improves the bioenergy status in the mouse liver. These findings may explain the efficacy of CordyMax Cs-4 in alleviating fatigue and improving physical endurance, especially in aged subjects. Treatment of mice with *C. militaris* lengthens the swimming time to exhaustion (Jung et al 2004). Koh et al (2003b) reported that the hot-water extract of *C. sinensis* mycelia prolongs swimming endurance capacity and produces an anti-fatigue action in mice.

Cordyceps is one of the components of Fuzheng Huayu recipe, which is used to control the development of post-hepatic cirrhosis or to prevent its complications (Liu et al 1996b).

The hot-water extract (30 mg kg^{-1} daily for 4 weeks), intracellular biopolymers and extracellular biopolymers of *C. sinensis* reduce the hepatic content of malondialdehyde and the serum concentrations of transaminases and alkaline phosphatase in rats with hepatic fibrosis induced by bile-duct ligation and scission. Treatment with extracellular biopolymers results in a reduction in hepatic hydroxyproline content and normalization of morphological characteristics of the liver, indicating an anti-fibrotic action (Nan et al 2001).

The effect of *C. sinensis* on hepatic fibrogenesis induced in rats by co-administration of CCl_4 and ethanol was studied by Liu & Shen (2003). It was found that *C. sinensis* delays cirrhotic development and improves liver function by inhibiting expression of transforming growth factor-β and platelet-derived growth factor and deposition of procollagen I and III. Zhou et al (1990) presented evidence for the beneficial effects of *C. sinensis* on chronic hepatitis B.

Hypolipidaemic activity

The polysaccharide CS-F30 from *C. sinensis* mycelia exhibits hypocholesterolaemic and hypotriglyceridaemic activity in mice (Kiho et al 1996). The water extract of cultured *C. sinensis* fruiting bodies prevents deposition of cholesterol in the aorta of atherosclerotic mice by inhibiting free-radical-mediated LDL oxidation (Yamaguchi et al 2000a). A hot-water extract of *C. sinensis* mycelia (150 or 300 mg kg^{-1}) lowers total cholesterol level, reduces the level of cholesterol carried by LDL and very-low-density lipoprotein, and elevates high density lipoprotein (HDL)-cholesterol level in the serum of mice fed a cholesterol-enriched diet (Koh et al 2003a).

Effect on the cardiovascular system

Feng et al (1987) reported the vasodilating effect of cultured *C. sinensis* mycelia in anaesthetized dogs. Chiou et al (2000) observed a hypotensive effect of an aqueous extract of *C. sinensis* (32 mg kg^{-1}) in anaesthetized rats and a vaso-

relaxant effect in isolated aorta. *C. sinensis* counteracts aconitine- or $BaCl_2$-induced arrhythmia in rats and increases the dosage of ouabain required to produce arrhythmia in guinea-pigs. It decreases the heart rate in anaesthetized rats and reduces the contractility of isolated papillary muscle or atria in guinea-pigs (Mei et al 1989).

An alcoholic extract of *C. sinensis* inhibits abdominal aortic thrombus formation in rabbits by preventing platelet aggregation (Zhao 1991).

Effect on lupus nephritis and systemic lupus erythematosus

The compound HI-A from *C. sinensis* reduces anti-ds-DNA production and lymphadenopathy, delays progression of proteinuria, improves kidney function and inhibits mesangial proliferation (Yang et al 1999). *C. sinensis* inhibits anti-ds-DNA production and improves survival in NZB/NZW F1 mice, a typical lupus animal model, indicating that *C. sinensis* may be beneficial to patients with systemic lupus erythematosus, an autoimmune disease with involvement of multiple organ systems (Chen et al 1993). *C. sinensis* inhibits lymphadenectasis, reduces proteinuria and plasma anti-ds-DNA antibody and improves renal function in MRL 1pr/1pr mice (Fu & Lin 2001). *C. sinensis*, at an oral dose of 2–4 g daily for 3 years, prevents the recurrence of lupus nephritis and protects renal function in lupus nephritis patients (Lu 2002).

Antibacterial, antifungal, antimalarial and insecticidal activity

Ophiocordin is an antifungal antibiotic isolated from submerged cultures of *C. ophioglossoides*. It is devoid of antibacterial activity (Kneifel et al 1977). Cordycepin inhibits the growth of *Clostridium paraputrificum* and *Clostridium perfringens*, but has no effect on *Bifidobacterium* spp. and *Lactobacillus* spp. (Ahn et al 2000). Cordypyridones A and B from *C. nipponica*, which are atropisomers of each other, demonstrate potent antimalarial activity in-vitro (Isaka et al 2001b). Cordycepin, at a dose of 500 mg L^{-1}, exerts larvicidal activity against *Plutella xylostella* after 2–4 days of treatment (Kim et al 2002).

DNase activity

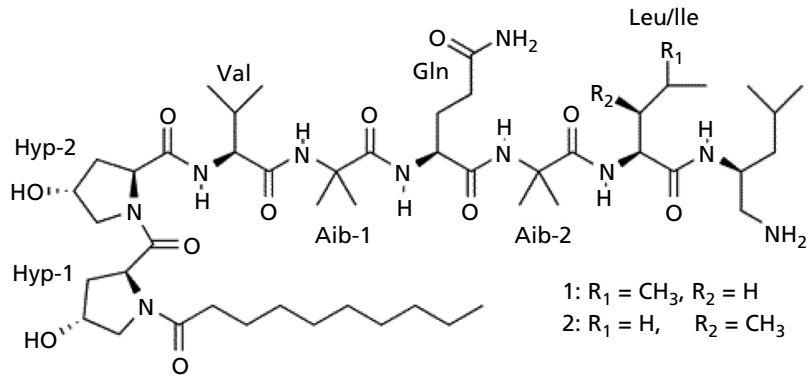
A single-chained acid DNase with a molecular mass of 34 kDa was purified from cultured *C. sinensis* mycelia. The DNase acts on both double-stranded and single-stranded DNA, but with a preference for the former. Its optimal pH is 5.5 and its optimal temperature is 55°C (Ye et al 2004).

Optimization of culture conditions for mycelial growth and production of polysaccharides and cordycepin

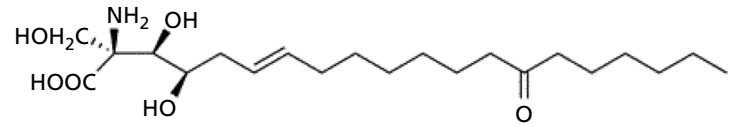
The conditions were described by Park et al (2001, 2002), Xu et al (2002), Kim et al (2003b, c), Xiao et al (2004), Mao & Zhong (2004) and Hsieh et al (2005).

Conclusion and future perspectives

It can be seen from this review that *Cordyceps* is beneficial to human health in a number of aspects since it possesses antidiabetic, anti-pathogenic, anti-tumour, immunomodulatory, antioxidative and anti-ageing activity. The active principles responsible for some of the aforementioned activity (Figure 1) have been chemically identified (Table 1). It is important to elucidate the chemical structures of the remaining active principles. It is possible that *Cordyceps* has pharmacological actions that remain to be discovered. The various *Cordyceps*



Cicadapeptin I (**1**) and cicadapeptin II (**2**)



Myriocin **3**

Figure 1 Structures of some *Cordyceps* constituents.

Table 1 Biological activity of *Cordyceps*

Biological activity	Chemical constituent/fraction	Representative reference(s)
Anti-inflammatory	Polysaccharide	Yu et al 2004a
	Methanolic extract	Kim et al 2003a
	Ethanolic extract	Woo & Park 2005
Antioxidant	Aqueous and ethanolic extracts	Yamaguchi et al 200oa, b
	Polysaccharide fraction	Li et al 2001a
Anti-tumour, anti-proliferative and anti-metastatic	Glucan	Yamada et al 1984
	Protein-bound-polysaccharide	Ohmori et al 1986
	Ergosterol peroxide	Bok et al 1999
	Galactosaminoglycan	Ohmori et al 1989a, b
	Exopolysaccharide	Zhang et al 2004b
	Cordycepin	Yoshikawa et al 2004
	Aqueous extract	Yoshida et al 1989
	Ethanolic extract	Xu et al 1992
Immunomodulatory	Aqueous methanol and methanol extracts	Went et al 2002
	Hot-water extract	Yu et al 2003
	Ergosterol peroxide	Kuo et al 2003
	Exopolysaccharide	Zhang et al 2004b
Steroidogenic	Polysaccharide	Huang et al 2001b
Hypoglycaemic	Polysaccharide	Kiho et al 1990
Hypolipidaemic	Polysaccharide	Kiho et al 1996
Anti-thrombotic	Water extract	Yamaguchi et al 2001a
Hepatic effects	Alcoholic extract	Zhao et al 1991
Renal effects	Hot-water extract	Nan et al 2001
Anti-lupus	HI-A	Lin et al 1999 Yang et al 1990
Insecticidal	Cordycepin	Kim et al 2002
Antimalarial	Cordypyridones A and B	Isaka et al 2001b
Antibacterial	Cordycepin	Ahn et al 2000
Antifungal	Ophiocordin	Kneifel et al 1977
DNAse	DNAse	Ye et al 2004

species can be differentiated by rDNA internal transcribed spacer analysis (Yue-Qin et al 2002). It would be worthwhile to compare the potencies of the various *Cordyceps* species in different bioassays.

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