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Chapter 5 Cordyceps as an Herbal Drug

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5.1. INTRODUCTION

Cordyceps is the composite of a genus of fungus that grows on the larva of insects. To date, more than 350 *Cordyceps-related* species have been found worldwide based on fungus and/or insect host. However, since 1964, only *Cordyceps sinensis* has been recorded officially as an herbal drug in Chinese pharmacopoeia. *C. sinensis*, known as *Dongchongxiacao* (winter-worm summer-grass) in Chinese, is one of the most famous traditional Chinese medicines and medicinal mushrooms. The fungus attacks the larva of some species of insects (Fam. *Hepialidae*), and converts each larva to a sclerotium, from which the fruiting body grows ([Figure 5.1](#)).

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FIGURE 5.1

(See color insert.) (a) *Cordyceps sinensis*, illustrated in the book *Ben Cao Bei Yao* by Wang Ang, which was published in 1694; (b) *C. sinensis* found in the soil (arrowhead indicates *C. sinensis*); and (c) collected as raw materials.

According to the theory of Chinese medicine, *C. sinensis* is sweet in taste and neutral in nature, and it can replenish the kidney, soothe the lung, stop bleeding, and eliminate phlegm. The fungus *C. sinensis* has been used for the treatment of fatigue, cough, hyposexuality, asthenia after severe illness, renal



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dysfunction, and renal failure ([State Pharmacopoeia Commission of PRC 2005](#)). In China, it is found in the soil of prairies at elevations of 3500–5000 m, mainly in the provinces of Qinghai, Tibet, Sichuan, Yunnan, and Gansu. In China, *C. sinensis* has been known and used as a remedy for more than 300 years. It was first recorded in *Ben Cao Bei Yao* by Wang Ang in 1694, and the Italian scholar Saccardo named the *Cordyceps* found in China officially as *Cordyceps sinensis* (Berk.) Sacc. in 1878; this nomenclature has been used ever since.

The ecosystem of *C. sinensis* has been terribly affected by the restriction of habitat and over- exploration. Although the Ordinance of Resources Protection on Wild Herbal Medicine was issued in 1987, the yield of natural *C. sinensis* is still decreasing. It was reported based on a survey conducted during June–July 2007 that the yield of natural *C. sinensis* decreased by more than 90% in the last 25 years. The price rocketed to more than 200,000 Renminbi (RMB)/kg (approximately US\$25,000) in 2007 ([Feng, Yang, and Li 2008](#)), and its usage was limited during the past decade by its limited supply.

Due to the rarity and outstanding curative effects of *C. sinensis*, some natural substitutes such as *C. militaris*, *C. liangshanensis*, *C. gunnii*, and *C. cicadicola* have been sold in markets ([Yang et al. 2009](#)). In addition, several cultured mycelia of *C. sinensis* and *C. militaris* fungi have become the main substitutes of the natural species as commercial products, and 50 medicines and two dietary supplements related to cultured Cordyceps have been approved by the State Food and Drug Administration of China since 2002 ([Feng, Yang, and Li 2008](#)). For example, JinShuiBao capsule, the commercial product of *C_s-4* (*Paecilomyces hepialid*, a standardized mycelium of *C. sinensis*), has been used in clinics throughout China. This product generates several million U.S. dollars every year. *Synnematum sinensis*, *Cephalosporium sinensis*, *Gliocladium roseum*, and *Mortierella hepialid*, the fungus strains isolated from natural *C. sinensis*, have also been subjected to large- scale fermentation and are used as commercial products ([Cheung, Li, and Tsim 2005](#)). Therefore, much effort has been invested in studying the evaluation of the quality, pharmacological activities, and clinical efficacies of natural and cultured cordyceps. In this chapter, we focus on the bioactivities, action mechanisms, and active ingredients of cordyceps, both natural and cultured.

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5.2. ANTITUMOR ACTIVITY

Cancer is the second leading cause of disease-related mortality throughout the world ([Xiao and Zhong 2007](#)). However, related therapy strategies are still limited to surgery, radiotherapy, and chemotherapy. Due to the limitations of surgery and radiotherapy and the side effects of chemotherapy, there is increasing interest in developing antitumor drugs from natural products. Studies have shown that cordyceps has antitumor activity in various

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cancers through several pathways. Both natural and cultured cordyceps have demonstrated antitumor effects ([Feng, Yang, and Li 2008](#); [Zhou et al. 2009a](#)).

Studies in vivo showed cordyceps had an inhibitory effect on Ehrlich ascites carcinoma and meth-A fibrosarcoma ([Ng and Wang 2005](#)), EL-4 lymphoma ([Yamaguchi et al. 1990](#)), B16 melanoma ([Wu, Zhang, and Leung 2007a](#)), Lewis lung carcinoma ([Nakamura et al. 1999](#)), and H22 tumors ([Chen et al. 2006](#)) in mice. Furthermore, *C. sinensis* reversed the suppressive effect of Taxol-induced leukopenia in mice, which indicated that *C. sinensis* could be used with other chemotherapy methods for cancer treatment ([Liu et al. 2008](#)). Cordyceps exhibited direct cytotoxic activity against several kinds of tumor cells, including Lewis lung carcinoma, B16 melanoma, lymphocytic (Jurkat), prostate (PC3), breast (MCF7), hepatocellular (HepG2, Hep3B), colorectal (HT-29) and HCT 116), and HL-60 cells ([Nakamura et al. 1999](#); [Wang et al. 2005](#); [Wu, Zhang, and Leung 2007a](#)). Although cordyceps had a cytotoxic effect on tumor cells, it did not show any cytotoxicity against normal cells ([Wu, Zhang, and Leung 2007a](#)).

Several mechanisms contribute to the antitumor effect of cordyceps, such as direct cytotoxicity, immunopotential, apoptosis, selective inhibition of ribonucleic acid (RNA), and protein synthesis, as well as antioxidant, antiangiogenic, antimutagenic, antimetastatic, and antiviral activities ([Xiao and Zhong 2007](#); [Feng, Yang, and Li 2008](#); [Zhou et al. 2009a](#)). Of them, the apoptotic homeostasis regulated by cordyceps might be the most important ([Buenz et al. 2005](#); [Feng, Yang, and Li 2008](#)) mechanism. The apoptotic molecular mechanism of cordyceps includes the activation of Bax, caspase-3 and/or -9, -8; inhibition of cyclooxygenase-2 (COX-2); and nuclear factor κ B (NF- κ B) protein expression and downregulation of Bcl-2 level ([Xiao and Zhong 2007](#); [Feng, Yang, and Li 2008](#)). Besides, apoptosis of MDA-MB-231 human breast carcinoma cells induced by *C. militaris* aqueous extract (0.8 mg/mL) was also associated with loss of mitochondrial membrane permeability. In addition, the extract decreased Akt activation and reversed PI3K/Akt-pathway-enhanced apoptosis ([Jin, Kim, and Choi 2008](#)). Furthermore, the apoptotic events induced by the extract were also mediated by diminished telomerase activity ([Park et al. 2009](#)).

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5.3. IMMUNOMODULATING EFFECT

The immune system protects human beings from infection with layered defenses of increasing specificity. First, physical barriers prevent pathogens from entering the body. If a pathogen breaks these barriers, the innate immune system provides an immediate, but nonspecific response. The human body possesses a third layer of protection, that is, the adaptive immune system. The adaptive immune response is activated by the response of the innate immune system. Cells of the innate system include phagocytes

(macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. In the adaptive system, B cells are involved in humoral immune response, whereas T cells contribute to cellular immune response. Immunopotentiating drugs are used to restore the immune system to normal and to reduce reoccurring and life-threatening infections. Immunosuppressive drugs are applied to control autoimmune disorders and inflammation when excessive tissue damage occurs, as well as to prevent transplant rejection after an organ transplant ([Taylor, Watson, and Bradley 2005](#)). Increasing evidence shows that cordyceps is a bidirectional modulator with both potentiating and suppressive effects on the immune system through regulating innate and adaptive immunity ([Li and Tsim 2004](#); [Ng and Wang 2005](#); [Feng, Yang, and Li 2008](#); ([Zhou et al. 2009a](#)).

5.3.1. POTENTIATION ACTIVITY

Natural *C. sinensis* has a long history of use in the treatment of respiratory infections and cancer. It has been postulated that the responsible mechanism is related to immune activation, particularly the promotion of innate immunity. The oral administration of *C. sinensis* extract improved the phagocytosis of macrophages in resting and cyclophosphamide-treated C57BL/6 mice implanted subcutaneously with syngeneic EL-4 lymphoma cells ([Yamaguchi et al. 1990](#)). Cultured *C. sinensis* induced production of interleukin (IL)-1 β , IL-6, IL-10, and tumor necrosis factor (TNF)- α ; elevated phagocytosis of human peripheral blood mononuclear cells (HPBMC); and elevated macrophage phagocytosis and monocyte production of H₂O₂. However, it did not induce cytokine overliberation in mice ([Ka et al. 2006](#)). Further study showed that an aqueous extract of mycelia of *C. sinensis* enhanced the IL-6, TNF- α , and nitric oxide (NO) release from primary murine macrophages by inducing mitogen-activated protein kinase (MAPK) pathways characteristic of inflammatory stimuli. The extract also synergized with interferon-gamma (IFN- γ) to stimulate cytokine production from macrophages, and the extract-treated mice spleens showed decreased bacterial burden compared to vehicle control. The results indicate that *C. sinensis* mycelia protected the animals from proliferation of bacteria by activating the macrophages ([Jordan, Sullivan, and Lee 2008a](#)). The *C. sinensis* could also enhance the activity of natural killer cells ([Ng and Wang 2005](#)). A *C. militaris* water extract induced phenotypic and functional maturation of dendritic cells, which then initiated T-cell responses against microbial pathogens and tumors ([Kim et al. 2006a](#)).

Cordyceps also promotes the adaptive immune system, including cellular and humoral immunity. Although natural and cultured *C. sinensis* methanol extracts had no effect on the proliferation of splenocytes and cytokine liberation such as IL-2 in primary mouse splenocytes in vitro ([Siu et al. 2004](#)) or in BALB/c mice in vivo ([Ka et al. 2006](#)), the extracts enhanced concanavalin A-stimulated proliferation and IL-2 level of mouse splenocytes in vitro at 200 μ g/mL ([Siu et al. 2004](#)) or ovalbumin-induced splenocyte

proliferation and serum immunoglobulin (Ig) G, IgG1, and IgG2b levels in ovalbumin-immunized mice ([Wu et al. 2006](#)). Cultured *C. sinensis* increased CD25 expression on lymphocytes in vitro ([Ka et al. 2006](#)), augmented numbers of CD4+ and CD8+ cells, improved CD4+/CD8+ ratio, and reduced IgA and IgG levels in patients with posthepatic cirrhosis ([Ng and Wang 2005](#)). Moreover, cordyceps had a regulatory effect on bronchoalveolar lavage fluids (BALF) cells. The *C. sinensis* ethanol extract could enhance Th₁ immune response, such as IFN- γ and IL-12 production, which could then inhibit IL-10 release from Th₂ cells and finally reduce IgE production from B lymphocytes. Reduced production of IgE would attenuate the occurrence of asthma attacks ([Kuo et al. 2001](#)). Fruiting bodies of *C. militaris* water extract significantly upregulated IL-18 gene expression, an inducer of IFN- γ in T cells and NK cells, in C57BL/6 mouse brain and liver in vivo and in RAW264.7 cells in vitro ([Kim et al. 2008](#)). Fruiting bodies, but not caterpillars, of *C. cicadae* methanol extract enhanced proliferation and IL-2 and IFN- γ production in phytohemagglutinin (PHA)-stimulated HPBMC ([Weng et al. 2002](#)).

5.3.2. SUPPRESSIVE EFFECT

Due to its inhibitory effect on the immune system, cordyceps can be used for treatment of autoimmune diseases and for immunosuppression after organ transplant. Early oral administration of *C. sinensis* (2.4 mg/g/day) induced the redistribution of HPBMC with reduced percentages of CD4+ T cells ($P < .05$), and attenuated the disease severity of lupus in (NZB/NZW) F1 mice with increased survival, decreased proteinuria, and reduced titers of anti-double-stranded DNA antibody ([Chen et al. 2009](#)). The administration of *C. sinensis* could augment the blocking effect of cyclosporin A on allogeneic graft rejection by reducing mononuclear cell infiltration in kidney grafts, CD4+ T cells in peripheral blood and serum IL-2, and IFN- γ production in an allograft kidney transplant rat model ([Ding et al. 2009](#)). Mycelia of *C. sinensis* water extract plus subtherapeutic cyclosporin A also decreased acute rejection in rats that had undergone heart transplant, completely ablated acute vasculopathy in mice at the dose of 50 mg/kg, and decreased IFN- γ release from mouse splenocytes and CD8+ T cells at 3.4 mg/mL in vitro ([Jordan, Hirsch, and Lee 2008b](#)).

Furthermore, cordyceps showed anti-inflammatory activity. Fruiting bodies of *C. sinensis* methanol extract inhibited PHA-stimulated lympho-proliferation and NK cells activity, and IL-2 and TNF- α release from HPBMC ([Kuo et al. 1996](#)). Chloroform and n-butanol fractions of the fruiting bodies of *C. sinensis* methanol extract inhibited the elevation of NO, inducible nitric oxide synthase (iNOS), TNF- α , and IL-12 in lipopolysaccharide (LPS)/IFN- γ -activated murine peritoneal macrophages in a dose-dependent manner in vitro ([Rao, Fang, and Tzeng 2007](#)). The administration of *C. militaris* decreased airway inflammation in ovalbumin-induced mice ([Hsu et al. 2008](#)), and had both anti-inflammatory activity on croton oil-induced mouse ear topical

edema and carrageenan-induced rat hind acute edema ([Won and Park 2005](#)). The administration of *C. pruinosa* methanol extract inhibited the production of IL- β , TNF- α , NO, and PGE₂ in LPS-stimulated macrophages at 10 μ g/mL in vitro and LPS-administered mice at 5 mg/kg in vivo via the suppression of NF- κ B activation ([Kim et al. 2003](#)). Methanol extract of caterpillars, but not fruiting bodies, of *C. cicadae* resulted in the suppression of proliferation of PHA-induced HPBMC and the lowering of IL-2, IL-4, IL-5, IFN- γ , and IL-12 release from PHA-stimulated HPBMC ([Weng et al. 2002](#)). So, different parts of cordyceps have different effects on immune response.

5.3.3. EFFECT ON GUT IMMUNE SYSTEM

The gastrointestinal tract plays a dual role in human physiology, that is, digestion and uptake of nutrients, and maintenance of immune homeostasis. The gastrointestinal-associated lymphoid tissue (GALT) is composed of Peyer's patches and other GALT such as lymphoid aggregates in the appendix, large intestine, and esophagus, tonsils, and adenoids. There are macrophages, dendritic cells, B lymphocytes, and T lymphocytes in GALT. Both innate and adaptive responses collaborate in maintaining the immune balance of GALT ([Huffnagle and Noverr 2008](#)). Although *C. sinensis* hot water extract had no direct effect on the proliferation of *Salmonella* sp., *Escherichia coli*, and *Lactobacillus* sp., it could significantly lower harmful bacteria populations (*Salmonella* sp. and *E. coli*.) and increase helpful bacteria numbers (*Lactobacillus* sp.) in the small intestine of broiler chicks administered with 600 mg/kg/day for 35 days ([Koh, Suh, and Ahn 2003a](#)). The results indicate that *C. sinensis* regulates intestinal bacteria by improving GALT or systemic immunity or both. The oral administration of cultured mycelia of *C. sinensis* hot water extract at 1 g/kg/day for 7 days stimulated the activation of peritoneal macrophages and Peyer's patch cells with increase in granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 levels in ICR mice ([Koh et al. 2002](#)). Macrophages in GALT function as antibacterial guards, by phagocytosing and killing any microbes that penetrate the lamina propria ([Macpherson, Marrinich, and Harris 2002](#)). Therefore, *C. sinensis* was supposed to promote the activity of macrophages in GALT. The fact that cytokines such as GM-CSF and IL-6 play an important role in systemic immune cells suggests that *C. sinensis* modulates the systemic immune system partly through a mechanism mediated by Peyer's patch cell ([Koh et al. 2002](#)). In mesenteric lymph node (MLN) lymphocytes, *C. sinensis* aqueous extract enhanced the secretion of IL-2 and IFN- γ from Th1 cells. Besides, the extract improved IgA release from resting and concanavalin A-stimulated MLN lymphocytes, whereas increased production of IgA at mucosal surfaces could promote an anti-inflammatory environment by neutralizing antigens ([Park et al. 2008](#)). Furthermore, *C. sinensis* and *C. scarabaecola* showed intestinal immune system modulating activity by activation of T lymphocytes in Peyer's patch ([Koh et al. 2002](#); [Yu, Kim, and Suh 2003](#)).

In summary, studies reveal that cordyceps has effects on both innate immunity and adaptive immunity. Furthermore, cordyceps also has a modulatory effect on gut immune system, which may further influence systemic immune function.

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5.4. ANTIOXIDANT ACTIVITY

Reactive oxygen species (ROS), including molecular oxygen (O_2), superoxide anion (O_2^-), H_2O_2 , hydroxyl radical (OH), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl; [Zhou, Mrowietz, and Rostami-Yazdi 2009b](#)), are well recognized as playing a dual role in biological systems, since they can be either beneficial or harmful to living systems ([Valko et al. 2004](#)). Normally, ROS form the natural by-products of aerobic metabolism and play a physiological role in cell signaling. However, the concentration of ROS can increase dramatically during times of environmental stress such as exposure to ultraviolet (UV) radiation or heat, causing damage to the lipids, proteins, and nucleic acids of cells. This injury to cell structures leads to several diseases, such as senescence, cancer, atherosclerosis and cardiovascular diseases, inflammatory lung diseases, immune dysfunction, and neurodegenerative disorders ([Rahman 2003](#); [Zhong 2006](#); [Valko et al. 2007](#)).

There is increasing evidence that cordyceps has antioxidant activity, which may be one of the mechanisms behind the antiaging, anticancer, anti-inflammatory, antiatherosclerosis, and immunomodulatory effects of cordyceps ([Table 5.1](#)). As far as different parts of *C. sinensis* are concerned, the fruiting bodies showed a similar potency with caterpillars in their antioxidant activities in xanthine oxidase assay, induction of hemolysis assay, and lipid-peroxidation assay ([Li et al. 2002](#)). The results also demonstrated that the caterpillar has a similar chemical composition to the fruiting body, which indicates that the function of the worm in cordyceps is to provide a growth medium for the fruiting body, and the caterpillar is eventually totally invaded by cordyceps mycelia ([Li et al. 2002](#)).

Cordyceps	Model	Route	Daily Dose	Concentration
Radiation				

[TABLE 5.1](#)

Antioxidant Activity In Vitro and In Vivo of Cordyceps.

Both water ([Li et al. 2001](#); [Yu et al. 2006](#); [Dong and Yao 2008](#)) and ethanol ([Wang et al. 2005](#); [Won and Park 2005](#); [Ra et al. 2008](#)) extracts of cordyceps showed significant antioxidant activity in vitro. However, the water extract exhibited a stronger inhibitory effect on superoxide anions and hydroxyl radicals than the ethanol extract ([Yamaguchi et al. 2000a](#)). Furthermore, both natural *C. sinensis* and cultured cordyceps showed direct and potent

antioxidant activities using in vitro assays, such as lipid-peroxidation assay, 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, and protein-peroxidation assay. Therefore, cultured cordyceps can be used for antioxidant activity, relieving human demands on natural *C. sinensis*, an endangered species ([Li et al. 2001](#); [Yu et al. 2006](#); [Dong and Yao 2008](#)).

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5.5. ANTIHYPERGLYCEMIC ACTIVITY

Cordyceps has hypoglycemic activity in normal animals. The oral administration of a cordyceps carbohydrate extract “Cs-4” at 2 g/kg/day for 25 days increased insulin sensitivity, and the extract had potential beneficial effects by maintaining whole-body glucose disposal with a less-pronounced increase in insulin secretion after a carbohydrate challenge in rats ([Balon, Jasman, and Zhu 2002](#)). In another study, normal rats fed with Cs-4 at 250 or 500 mg/kg/day for 17 days showed significant decreases in fasting blood glucose level by 27% and 24%, respectively, and the fasting plasma insulin of rats in the 500-mg/kg group decreased by 37%. Furthermore, oral glucose tolerance tests demonstrated that the extract significantly improved glucose tolerance at 0.5, 1.0, and 2.0 hours after ingestion of glucose ([Zhao et al. 2002](#)).

Cordyceps also showed an antihyperglycemic effect in diabetic animals. Although fruiting bodies of natural *C. sinensis* (4 g/kg/day) had no effect on the fasting insulin level in diabetic rats ([Lo et al. 2004](#)), it improved the weight and attenuated water intake (day 15 to day 29), fasting blood glucose level (day 15 to day 26), and serum concentration of fructosamine (day 29) in diabetic rats. Fruiting bodies of *C. sinensis* also improved thymus weight and glucose tolerance (day 26; [Lo et al. 2004](#) and [2006](#)). However, in this experiment, *C. sinensis* had no effect on serum triglycerides and cholesterol concentrations of diabetic rats ([Lo et al. 2004](#)). [Choi et al. \(2004\)](#) also found that the aqueous extract of cultured *C. militaris* had no effect on fasting insulin level or glucose uptake in the gastrointestinal tract. However, the extract was found to lower fasting serum glucose level, reduce triglycerides level in soleus muscles, increase the whole-body glucose disposal rate, as well as enhance glucose transporter 4 (GLUT 4) content and fraction velocity of glycogen synthase in the soleus and quadriceps muscles in 90% pancreatectomized rats that were fed *C. militaris* extract at 500 mg/kg/day for 8 weeks ([Choi et al. 2004](#)).

Interestingly, fruiting bodies, not caterpillars, of *C. sinensis* had an effect on lowering the fasting blood glucose level and increasing the thymus weight ([Lo et al. 2004](#)). However, fermented mycelia and broth of *C. sinensis* had similar antihyperglycemic effect with fruiting bodies in nicotinamide and streptozotocin-induced diabetic rats ([Lo et al. 2006](#)). Therefore, the fermented products of cordyceps can be developed as potential antidiabetic agents or functional foods for persons with a high risk of diabetes mellitus.

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5.6. SEXUAL AND REPRODUCTIVE FUNCTION ENHANCEMENT ACTIVITY

Testosterone is necessary for normal sperm development. It activates genes in Sertoli cells, which promote differentiation of spermatogonia. Cordyceps has traditionally been used for the enhancement of sexual function in human beings. Evidence shows that *C. sinensis* and *C. militaris* can improve reproductive activity and restore impaired reproductive function ([Table 5.2](#)). The administration of *C. sinensis* enhanced libido and sexual activity, and restored impaired reproductive function in both sexes in human ([Zhu, Halpern, and Jones 1998](#)). Such effects are related to the enhancement of testosterone release in plasma through cAMP (adenosine monophosphate)-protein kinase A signal pathway ([Hsu et al. 2003a](#)). Fractions of cultured mycelia of *C. sinensis* with water-soluble low-molecular-weight proteins and polysaccharides of relatively poor water solubility and protein, but not fractions with water-soluble low-molecular-weight polysaccharides, increased testosterone levels in mice ([Hsu et al. 2003b](#); [Huang et al. 2004](#)). A protein in *C. sinensis* contributed to the observed hypotensive and vasorelaxant properties by improving the production of NO ([Chiou et al. 2000](#)); this protein might help the penis trap blood for erection, thereby improving sexual function ([Drewes, George, and Khan 2003](#)).

Cordyceps	Model	Daily Dose or Concentration	Ref.
Cultured <i>C. sinensis</i>	Fruiting bodies	0.52.0 g/kg	21
Mycelia	Male mice	0.02 or 0.2 mg/kg	71

[TABLE 5.2](#)

Effect of *C. sinensis* and *C. militaris* on Sexual and Reproductive Function.

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5.7. ANTIFATIGUE ACTIVITY

Fatigue is defined as difficulty in initiating or sustaining voluntary activity ([Chaudhuri and Behan 2004](#)), and can be classified into mental and physical fatigue ([Mizuno et al. 2008](#)). Fatigue is a common symptom in sickness and in health. Chronic fatigue can affect an individual's performance. In addition, long-term accumulated fatigue can lead to *karoshi* (a Japanese word meaning death as a result of overwork). In China, cordyceps is used to restore health after various diseases and to hasten recovery from exhaustion because of its adaptogenic (antistress) properties and ability to enhance endurance and strength ([Bucci 2000](#)).

Oral administration of *C. sinensis* mycelia water extract at 150 mg/kg/day for 7 days ([Koh et al. 2003b](#)) or ingestion of fruiting bodies of *C. militaris* at 500 mg/kg/day for 4 weeks ([Jung, Kim, and Han 2004](#)) significantly prolonged the swimming time of mice by about 20 and 24 minutes, respectively. This effect was related to the enhancement of immunity. The administration of *C.*

sinensis at 150 mg/kg/day for 8 days inhibited the increase of total cholesterol and the decrease of alkaline phosphatase in rats, as well as significantly reversed the decreased weight of liver, adrenal gland, thymus, and thyroid ([Koh et al. 2003b](#)). The involvement of cordyceps in adenosine triphosphate (ATP) production also accounts for a decrease in physical fatigue when it is administered. The oral administration of cultured *C. sinensis* extract (200 mg/kg/day, p.o.) not only improved hepatic energy metabolism and blood flow in dietary hypoferric anemic mice for 4 weeks ([Manabe et al. 2000](#)) but also increased significantly the ATP/inorganic phosphate ratio in the liver of normal mice for 3 weeks ([Manabe et al. 1996](#)) or for 7 days ([Dai et al. 2001](#)) with no steatosis, necrosis, inflammation, or fibrosis in the liver specimens ([Manabe et al. 1996](#) and [2000](#)). Treatment with natural or cultured cordyceps extracts (1 g/kg/day, p.o.) for 3 days enhanced myocardial ATP generation capacity *ex vivo* in mice by 29% and 32%, respectively, which might be mediated by the enhancement of mitochondrial electron transport ([Siu et al. 2004](#)).

Patients having chronic fatigue syndrome often have depression. Around 30–70% of such patients show the features of major depression ([Adler 2004](#)). Supercritical fluid extract (SCCS, 2.5–10 mL/kg, p.o.), other than hot water extract (500–2000 mg/kg, p.o.), of *C. sinensis* show significant antidepressant-like activity. After 5 days of administration, SCCS shortened immobility times in the mouse-tail suspension test, although it had no effect on locomotor activity in the mouse open field test. It was considered that SCCS played an antidepressant-like role by affecting the adrenergic and dopaminergic systems other than the serotonergic system ([Nishizawa et al. 2007](#)). In addition, cordyceps has a powerful antioxidant effect, which may eliminate the ROS produced in working muscles during exercise and help in relieving fatigue ([Mizuno et al. 2008](#)). Finally, *C. sinensis* induced a more efficient utilization and consumption of O₂, which resulted in a greater survival rate under a hypoxic environment ([Lou, Liao, and Lu 1986](#)) in mice. The results indicate a more efficient use of O₂ by cordyceps to support essential physiological activities of tissues and improve tolerance to hypoxia-induced acidosis. However, few clinical trials have been conducted on the antifatigue effect of cordyceps, and most of the conducted tests were methodologically flawed, especially in the inclusion of other drugs in the experiments. For instance, capsules containing Cs-4, *Rhodiola rosea*, and other ingredients did not enhance muscle-tissue oxygen saturation ([Colson et al. 2005](#)) and cycling performance ([Earnest et al. 2004](#)) in healthy men. Similarly, ingestion of a supplement containing cultured *C. sinensis*, adenylypyrophosphoric acid, calcium pyruvate, and yohimbine hydrochloride once 1 hour before a sport activity showed no ergogenic effects in healthy men ([Herda et al. 2008](#)). One reason may be that the ingestion schema of *C. sinensis* was insufficient to elicit positive changes in humans. A 1-week loading phase followed by at least a 2–4-week maintenance phase may be needed to obtain the effect of promoting aerobic capacity and resistance to

fatigue. Another reason may be that as these experiments were performed on healthy persons, there were fewer margins for physiological, health, and performance improvement than in diseased or elderly persons ([Colson et al. 2005](#)).

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5.8. PROTECTIVE EFFECT ON THE KIDNEY

C. sinensis has been used for the treatment of renal diseases, such as chronic nephritis, chronic pyelonephritis, chronic renal dysfunction or failure, and nephritic syndrome ([Feng, Yang, and Li 2008](#)). The *C. sinensis* extract significantly improved renal function via antiapoptotic and anti-inflammatory activity in rats subjected to 60 minutes of ischemia and following 3 days of reperfusion of the kidneys. Downregulation of the apoptotic gene of caspase-3 accompanied the decreases in inflammatory genes such as MCP-1, TNF- α , and iNOS. The result indicates that *C. sinensis* plays a potential therapeutic role in renal transplantation ([Shahed, Kim, and Shoskes 2001](#)).

Another mechanism by which cordyceps protects the kidney is its inhibitory effect on mesangial cell proliferation. It has been suggested that glomerular sclerosis is preceded by proliferation of mesangial cells that exhibit smooth muscle cell features and accumulation of mesangial extracellular matrix. Both *C. sinensis* and *C. militaris*, at a concentration of 100 mg/mL, significantly reversed the proliferation of human mesangial cell stimulated by low-density lipoprotein (LDL; [Wu, Wang, and Cheng 2000](#)). Moreover, *C. sinensis* could protect the kidney from cyclosporine A-induced chronic nephrotoxicity, with lower blood urea nitrogen (BUN), interstitial edema and fibrosis, and bulbular necrosis ([Wojcikowski, Johnson, and Gobë 2006](#)). Furthermore, administration of a water extract of cordyceps had a protective effect in rats with acute renal failure induced by gentamicin. The possible mechanisms include protection of sodium pump activity, lowering of lipoperoxidation in tubular cells, and attenuation of lysosomal overactivity in tubular cells ([Ng and Wang 2005](#); [Li and Yang 2008a](#)). In addition, *C. sinensis* enhanced cellular immunity in rats with chronic renal failure ([Cheng 1992](#)).

Clinical trials have also shown some evidence for the use of cordyceps as a renoprotectant remedy ([Wojcikowski, Johnson, and Gobë 2004](#) and [2006](#)). For example, Bailing capsule, a preparation made from *C. sinensis* mycelia, ameliorated the rejection of renal transplant, improved renal and liver function, regulated hypoproteinemia and hyperlipidemia, stimulated hemopoietic function, and decreased the incidence of infections in patients after renal transplant ([Sun et al. 2004](#); [Li et al. 2009](#)). In patients with chronic renal failure, ingestion of another cordyceps product Cs-4, called JinShuiBao, also significantly promoted renal function, which decreased serum urea and creatinine and increased total blood protein and calcium ([Feng, Yang, and Li 2008](#)).

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5.9. EFFECT ON THE LIVER

Cordyceps has been used in clinical practice for the treatment of chronic hepatitis and related diseases ([Zhao 2000](#)). There are several ways in which it contributes to the treatment of and protection against liver disease. First, cordyceps has a potential enhancing effect on the immunological function of patients suffering from chronic hepatitis B ([Gong, Wang, and Tang 2000](#)) and from posthepatic cirrhosis ([Zhu and Liu 1992](#)). Second, cordyceps was shown to inhibit and reverse liver fibrosis via degradation of collagen in rats with liver cirrhosis induced by dimethylnitrosamine ([Li et al. 2006a](#); [Wang, Liu, and Tang 2008](#)), inhibit proliferation of hepatic stellate cells in vitro ([Chor et al. 2005](#)), downregulate intercellular adhesion molecule-I (an index of liver fibrogenesis) and CD126 in human fibroblasts ([Li and Tsim 2004](#)), and decrease expression of transforming growth factor- β and platelet-driven growth factor ([Liu and Shen 2003](#)). Third, cordyceps decreased lipid peroxide levels in serum and hepatic tissue, and lowered serum TNF- α in bacillus calmette guerin plus LPS-induced liver injury in mice ([Zeng, Tang, and Yuan 2001](#)).

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5.10. ACTIVE COMPONENTS

Many active ingredients, such as cordycepin, polysaccharides, and ergosterol, have been isolated from various *Cordyceps* species and account for a range of bioactivities ([Table 5.3](#)).

Compound	Source	Bioactive Nucleoside No.
Cordycepin	Cultured <i>C. militaris</i>	Anticancer

[TABLE 5.3](#)

Chemical Compounds in Cordyceps and Their Pharmacological Activities.

5.10.1. NUCLEOSIDES AND THEIR ACTIVITIES

Nucleosides are one of the major ingredients in cordyceps. To date, more than 10 nucleosides and their related components, including adenine, adenosine, cytidine, cytosine, guanine, guanosine, uracil, uridine, hypoxanthine, inosine, thymine, thymidine, 2'-deoxyuridine, 2'-deoxyadenosine, cordycepin, N⁶-methyladenosine, and 6-hydroxyethyl-adenosine, have been isolated and/or identified in cordyceps ([Feng, Yang, and Li 2008](#)). Adenosine A₁, A_{2A}, A_{2B}, and A₃ receptors are distributed in the brain, lung, heart, liver, and kidney, and are involved in central nervous system (CNS)-mediated events such as sleep, immunological response, respiratory regulation, cardiovascular function, and liver and kidney activity ([Li and Yang 2008a](#)). Interestingly, the pharmacological effects of cordyceps match well with the distribution and physiological roles of adenosine

receptors, including anticancer, antiaging, antithrombosis, antiarrhythmias, and antihypertension; immunomodulatory activity; and protective effects on the kidney, liver, and lung ([Li and Yang 2008a](#)).

Macrophages express adenosine A_{2A}, A_{2B}, and A₃ receptors. Activation of these receptors results in the upregulation of IL-10; downregulation of IL-12 and TNF- α and increase of vascular endothelial growth factor (VEGF), macrophage inflammatory protein (MIP)-1 α , and NO, respectively ([Kumar and Sharma 2009](#)). The ratio of uridine:inosine:guanosine at 8:11:5, which is the ratio of natural *C. sinensis*, showed an enhancement effect on the release of NO, TNF- α , and IL-1 from resting primary mouse macrophages, whereas it had no effect on LPS-stimulated cells ([Li and Yang 2008b](#)). However, uridine:adenosine:guanosine at a ratio of 11:7:9, the ratio found in cultured *C. sinensis*, improved NO, TNF- α , and IL-1 production in resting macrophages while suppressing the release of cytokine from LPS-stimulated cells ([Li and Yang 2008c](#)). The results indicate that different components act on different subreceptors; therefore, different ratios of these nucleosides result in different immune responses in macrophages.

Cordycepin was isolated from cultured *C. militaris* in 1950 ([Cunningham et al. 1950](#)), and was identified as 3'-deoxyadenosine in 1964 ([Kaczka et al. 1964](#)). It mainly exists in cultured *C. militaris*, and there is little in natural and none in cultured *C. sinensis* ([Feng, Yang, and Li 2008](#)). Cordycepin possesses anticancer, immunomodulating, and antioxidant abilities. Ongoing phase I/II clinical trials are investigating cordycepin in the treatment of TdT-positive acute lymphocytic leukemia. A study demonstrated that cordycepin showed a cytotoxic effect on tumor cells. The growth of B16 cells was inhibited by 60 μ M of cordycepin by 70.1% at 72 hours, and this effect was induced by stimulating adenosine A₃ receptors followed by the signaling pathway of GSK-3 β activation and cyclin D1 inhibition ([Yoshikawa et al. 2008](#)). Furthermore, Won et al. found that cordycepin diminished the production of ROS (O₂⁻, and H₂O₂) in platelet-derived growth factor-BB (PDGF-BB)-induced vascular smooth muscle cells in vitro, which helped inhibit the neointima formation and vascular sprout outgrowth in response to PDGF-BB. The A₁/A₂ adenosine-receptor antagonist dipropyl-8-sulphophenylxanthine (DPSPX; 10 nM, 60 minutes) reversed the inhibition of PDGF-BB-induced migration evoked by cordycepin. The A₁/A₂ receptors are widely expressed in vascular cells and exert cardioprotective effects. Therefore, cordycepin may act as an antiatherosclerotic agent by activating the A₁/A₂ receptor ([Won et al. 2009](#)).

5.10.2. STEROLS AND THEIR ACTIVITIES

Several sterols, including ergosterol, H1-A, Δ^3 ergosterol, ergosterol peroxide, ergosteryl-3- β -D-glucopyranoside, cereisterol, β -sitosterol, daucosterol, cholesterol, 22, 23-dihydroergosteryl-3-O- β -D-glucopyranoside, cholesteryl palmitate, campesterol, and dihydrobrassicasterol, have been identified in

cordyceps ([Feng, Yang, and Li 2008](#)). Ergosterol exists in both free and combined forms in cordyceps, and the content of the free form is fairly high in both natural and cultured cordyceps ([Yang et al. 2009](#)). Ergosterol is a biological precursor of vitamin D₂, needed for bone development in humans. The sterol β -sitosterol is found mainly in natural cordyceps and commercial cultured *C. sinensis*, whereas it is lacking in commercial cultured *C. militaris* and cultured *C. sinensis* in Yang's laboratory ([Yang et al. 2009](#)). In Europe, P-sitosterol plays a major role in the treatment of benign prostatic hypertrophy ([Wilt et al. 2000](#)). Phytosterols, especially β -sitosterol, play a protective role against colon, prostate, and breast cancer ([Awad et al. 2000](#)). Moreover, phytosterols, mainly β -sitosterol, campesterol, and stigmasterol, decrease cholesterol absorption while being poorly absorbed themselves ([Ostlund 2007](#)). The bioactivities of sterols are helpful in elucidating some therapeutic indications of cordyceps such as in hyperlipidemia and cancer.

5.10.3. FREE FATTY ACIDS AND THEIR ACTIVITIES

Ten free fatty acids (FFAs), that is, lauric acid, myristic acid, pentadecanoic acid, palmitoleic acid, palmitic acid, linoleic acid, oleic acid, stearic acid, docosanoic acid, and lignoceric acid, have been found in natural *C. sinensis*, *C. liangshanensis*, and *C. gunnii*, as well as in cultured *C. sinensis* and *C. militaris*. Among these FFAs, palmitic acid, linoleic acid, oleic acid, and stearic acid are the major components in natural and cultured cordyceps. Natural cordyceps contains more palmitic acid and oleic acid than cultured ([Yang et al. 2009](#)). The FFAs are not only essential nutritional compounds but also modulators of many cellular functions through their receptors. The FFA receptors are G-protein-coupled receptors, including G-protein receptor (GPR) 40, GPR41, GPR43, GPR120, and GPR84 ([Rayasam et al. 2007](#); [Hirasawa et al. 2008](#); [Swaminath 2008](#)). The activation of FFA receptors exhibits several physiological effects ([Table 5.4](#)); they, therefore, are purported to be novel therapeutic targets for diabetes, dyslipidemia, and immunomodulation, especially type 2 diabetes.

Subtype	Apoptosis	G-protein Coupling	Tissue
GPR40 (C16)	Medium-long chain, C12-C16	Gq/11	Pancreas, testis, I
GPR120 (C18:1)	Short chain, C3-C16	G12/13	Intestine, adipose, and immune

TABLE 5.4

Summary of Free Fatty Acid Receptor Ligands and Physiological Roles in Various Tissues.

Pentadecanoic acid (C15) and palmitic acid (C16) are the most potent FFAs on GPR40, and can activate the GPR40 receptor and stimulate calcium release ([Briscoe et al. 2003](#)). This, in turn, triggers insulin release from the β -cells of the pancreas, thus producing a hypoglycemic effect. Both these FFAs exist in both wild and cultured cordyceps, palmitic acid being a main ingredient, and palmitic acid may be one of the active hypoglycemic

components in cordyceps. On the other hand, FFAs in cordyceps may also indirectly promote glucose-stimulated insulin secretion and then inhibit plasma glucose level by activation of GPR120 in the intestinal tract ([Hirasawa et al. 2008](#)). The receptors GPR41, GPR43, and GPR84 are expressed on immune cells. Activation of these receptors by FFAs induces an immunomodulatory effect ([Swaminath 2008](#)) and cordyceps contains FFAs and possesses significant relevant activity, indicating that the FFAs in the cordyceps contribute to its immunomodulatory mechanisms.

5.10.4. CARBOHYDRATES AND THEIR ACTIVITIES

Cordyceps not only contains a high amount of polysaccharides, ranging from 3–8% of the total dry weight, but also contains a high amount of D-mannitol. D-mannitol, also called cordycepic acid, was isolated from *C. sinensis* in 1957. It is one of the major compounds in natural and cultured cordyceps, which contributes over 3.4% ([Li and Yang 2008a](#)) and 2.4% ([Feng, Yang, and Li 2008](#)) of total dry weight, respectively. Due to its osmotic activity, D-mannitol has long been used for the treatment of cerebral edema and refractory intracranial hypertension in traumatic brain injury, subarachnoid hemorrhage, and stroke ([Rangel-Castilla, Gopinath, and Robertson 2008](#)), as well as in acute renal failure ([Lameire, De Vriese, and Vanholder 2003](#)). The inhalation of dry, powdered mannitol is a useful therapeutic agent for patients with cystic fibrosis ([Jaques et al. 2008](#)) and bronchiectasis ([Ilowite, Spiegler, and Chawla 2008](#)); the inhaled powder increases mucociliary clearance by rehydrating the airway. Mannitol is also used as a diagnostic test for airway hyper-responsiveness to help in the diagnosis of asthma ([Anderson et al. 2009](#)). These pharmacological effects of D-mannitol can thus be one important reason for cordyceps being used to treat some respiratory diseases such as asthma and chronic bronchitis, renal dysfunction and renal failure, and hypertension.

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5.11. CONCLUSIONS

C. sinensis is a valued traditional Chinese medicine. Because it is rare and expensive, several other natural cordyceps, cultured mycelia, and fruiting bodies of cordyceps have become its main substitutes in commercial health food formulations. Experiments have shown that cordyceps has several bioactivities, such as antitumor, immunomodulatory, antioxidant, sexual and reproductive function enhancement, hypoglycemic, and antifatigue activities, and have a protective effect on the kidney and liver. Different compounds contribute to different bioactivities. Normally, the cultured mycelia of cordyceps are as effective as those found in natural cordyceps. Cordyceps is quite safe in the in vivo treatment of animals for up to 3 weeks. Fermented products of cordyceps, along with natural *C. sinensis*, could be potential agents or functional foods for maintaining human health.

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