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# The Scientific Rediscovery of an Ancient Chinese Herbal Medicine: *Cordyceps sinensis*

**Part I**

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## ABSTRACT

This review presents *Cordyceps sinensis* (Berk.) Sacc., a fungus highly valued in China as a tonic food and herbal medicine. The extant records show the continued use of *C. sinensis* is now centuries old. The major chemical, pharmacological, and toxicological studies on *C. sinensis* and the various derived, cultured, fermented mycelial products currently in use are reviewed from the English and Chinese literature. Preclinical in vitro and in vivo studies and clinical blinded or open-label trials in to date over 2000 patients are reviewed. These studies show the main activities of the fungus in oxygen-free radical scavenging, anti senescence, endocrine, hypolipidemic, antiatherosclerotic, and sexual function-restorative activities. The safety of the fungus, its effects on the nervous system, glucose metabolism, respiratory, hepatic, cardiovascular, and immune systems, immunologic disease, inflammatory conditions, cancer, and diseases of the kidney will be reviewed in the second part of this article to be published in the winter issue of this journal.

## INTRODUCTION

Cordyceps (*Cordyceps sinensis* [Berk.] Sacc.), also known as Chinese caterpillar fungus or "DongChongXiaCao" (summer-plant, winter-worm), is one of the most valued Chinese medicinal herbs (Figs. 1 and 2). It was initially recorded in Ben-Cao-Cong-Xin (New Compilation of Materia Medica) by Wu-Yiluo during the Qing Dynasty (1757 ao). According to traditional Chinese medicine (TCM), Cordyceps goes to the "Lung" meridian and the "Kidney" meridian (see below) and provides "lung protection,' "kidney improvement," and "Yin Yang double invigoration."

## THE "KIDNEY" AND "LUNG" IN TCM

Although we are not practitioners of TCM,we have included brief explanations of some of the organ concepts mentioned in this review that, however, archaic to those of us trained in

Western physiology and pathology, were and continue to be applied in traditional prescriptions of Cordyceps. The kidneys are known as "the root of life" in TCM, for they store 'Jing,' a substance described as an undifferentiated, prime organic material that is neither yin nor yang and is "the source of reproduction, development, and maturation'' (Kaptchuk, 1983). Author and practitioner Ted J. Kaptchuk, O.M.D., in his now classic Western book on TCM, The Web that has no Weaver:
Understanding Chinese Medicine, explains the role of the kidneys and the jing as follows:

*Conception is made possible by the power of Jing; growth to maturity is the blossoming of Jing; and the decline into old age reflects the weakening of Jing. As time passes, the Jing decreases in both vitality and quantity. Because the Kidneys store Jing, all these processes are governed by the Kidneys. Therefore, reproductive problems such as sterility or impotence and developmental disorders like retarded growth or lack of sexual maturation are seen as dysfunction of the Kidney's storing of Jing (Kaptchuk, 1983).*

Further to the kidneys, Kaptchuk relates that in TCM the understanding is that they have rulership over the bones and produce the bone marrow. And although the lungs are the administrators of respiration, "normal breathing also requires assistance from the Kidneys." Here, Kaptchuk enters the subject of Qi or chi, the fundamental "energy of life" that the ancients differentiated into different forms, Kaptchuk writes,

*The Kidneys enable the Natural Air Qi to penetrate deeply, completing the inhalation process by what is called "grasping the Qi." The Kidneys are thus the root of Qi,' while the Lungs are the "foundation of Qi." Proper breathing thus depends on the Kidneys; and Kidney disharmonies may result in respiratory problems, especially chronic asthma" (Kaptchuk, 1983).*

The other meridian that Cordyceps is said to "go to" in TCM is that of the "Lung." The lungs are said to regulate "the Qi of the entire body" and to rule the Qi (Kaptchuk, 1983)." Kaptchuk explains:

*The Lungs take in the Natural Air Qi, propelling it downward by their descending property. This is inhalation. The disseminating property, which "makes things go 'round,'" allows for exhalation, the expulsion of "impure" air. When the lungs are healthy, the Qi enters and leaves smoothly, and respiration is even and regular. When an imbalance or obstruction interferes with the Lungs, impairing either the descending or the disseminating functions, symptoms such as cough, dyspnea, asthma, or chest distention may result (Kaptchuk, 1983).*

When there is a "disharmony of the Lungs," it is said that stagnant Qi or deficient Qi can result in any area of the body. And if the Qi of the lungs is found to be weak, sweat may be found either insufficient or too profuse and the power of resistance of the "Protective Qi will be poor." Kaptchuk (1983) writes that the "throat is said to be the 'door' of the Lungs and the 'home' of the vocal cords, so both the throat and vocal cords are also related to the Lungs. Many common nose and throat disor- ders are therefore treated through the Lungs." For centuries, the fruit body and attached mycelium of Cordyceps have been the herb of choice in China to treat "lung" and "kidney" asthenia syndromes (TCM terms describing groups of symptoms associated with respiratory and renal diseases and other disease con- ditions) (Table 1). They have been included as a dietary supplement to maintain health and prevent disease (Table 2) (Jiang, 1993; 1994). In the West, Cordyceps only recently received attention after Chinese female runners established several world long-distance records (1500 to 10,000 meters) within a short period of time in 1993. The athletes' coach attributed their success in part to a special Cordyceps-containing diet that enhanced their physical performance and endurance (Ma, 1997).

**Table 1. Medicinal Uses of Cordyceps**

| |
|---|
| Fatigue |
| Night Sweating |
| Male and Female Hyposexualities, including Impotence |
| Hyperglycemia |
| Hyperlipidemia |
| Asthenia after Severe Illness |
| Respiratory Diseases |
| Renal Dysfunction and Renal Failure |
| Arrhythmias and other Heart Disease |
| Liver Disease |

NOTE: See references in corresponding sections of review, parts 1 and 2.

## DESCRIPTION

Cordyceps is a unique black, blade- shaped fungus found primarily at high altitude on the Qinghai-Tibetan plateau. The fungus is parasitic, growing on and deriving nutrients from several species of caterpillar, although primarily that of the moth Hepialus armoricanus Oberthur, which lives 6 inches underground (Chen and Jin, 1992; Yin and Tang, 1995). In late autumn, chemicals on the skin of the caterpillars interact with the fungal spores and release the fungal mycelia, which then infect the caterpillar. By early summer of the following year, the fungal infestation has killed the caterpillar and the fruiting body can be seen protruding from the caterpillar's head. This wild form, *Cordyceps sinensis*, is harvested, whereas the principal fungal mycelium of Cordyceps sinensis, known as Paecilomyces hepiali Chen, is cultivated aseptically (Yue et al., 1995).

Because natural Cordyceps (wild *Cordyceps sinensis*) is rare, Chinese scientists have extensively examined its lite cycle with the aim of developing a technique for isolating fermentable stratus of *Cordyceps sinensis*. At the Institute of Materia Medica, Chinese Academy of Medical Sciences, one result of this research has been the isolation of the strain Cs-4 from wild *Cordyceps sinensis* (Berk.) Sacc. Cs-4 has been used to produce a fermented product of the mycelia of Paecilomyces hepiali Chen and contains pharmacologically active components similar to those of the natural Cordyceps. Since its successful isolation in 1982, the Cs4 fermentation product has been studied intensively in China. Industrial fermentation methodology (resulting m a commercial product, JinShuiBao capsule). Chemical composition, therapeutic functions, and toxicity have been thoroughly investigated, and basic research in animals has carried out. JinShuiBao capsule, the Cs-4 fermentation product, has received approval by the National New Drug Review and Approval committee of the Chinese Ministry. of Public Health, and has been used in clinics throughout China for the indications listed in Table 1.

**TABLE 2. DIETARY USES OF CORDYCEPS IN MEDICINAL DISHES**

| | |
|---|---|
| **Cooked with an old duck** | For patients with Cancer, Asthenia, or after severe illness |
| **Cooked with hen** | For hyposexuality (especially emission) |
| **Cooked with black-bone hen** | For Asthenia (especially Qi-Yin asthenia) |
| **Cooked with lean pork** | For Fatigue, Male Impotence, and Kidney Asthenia |
| **Cooked with sparrow** | For antiaging/senescence |
| **Cooked with quail** | For Fatigue, Poor Appetite, "Kidney" Asthenia, and Tuberculosis |
| **Cooked with steamed turtle** | For Male/Female Hyposexuality |
| **Cooked with baked abalone** | For Chronic Bronchitis, COPD, Tuberculosis, Arteriosclerosis, Cataracts, and for Healthy individuals in any season |

Data adapted from Jiang (1984)

In total, more than 2000 patients with various medical disorders have been revolved in clinical trials of Cs-4 in China. The results of these clinical studies (blinded or open- labeled) indicate that Cs-4 is very effective and safe, and very similar to the parental, natural Cordyceps in the amelioration of conditions, with only few and mild side effects. Besides Cs-4, several mycelial strains have been isolated from natural Cordyceps and some of them are manufactured with fermentation technology (Yin and Tang, 1995). For instance, sinensis (or Cephalosporium donqchongxiacao), a nonsexual phase strain of Cordyceps known as NingXinBao, XinGanBao, and other names, was isolated by the QingHai Institute of Livestock and Veterinary Sciences. Cn80-2 (Paecilomyces sinensis), another nonsexual phase strain, was isolated by FuJian QingLiu County Hospital and Institute of Microbiology, Chinese Academy of Sciences. SMIH8819 is a product of Sanming Mycological Institute, Fujian, China. 832 (Scydalilum sp.) was isolated by the Navy Institute of Medicine. Hirsutella sinensis, Mortierella hepiali Chen lu sp. nov., Scytalidium hepiali G. L. Lisp. nov., Tolypocladium sinensis C.I. sp. nov., and others have been isolated natural Cordyceps (Yin and Tang, 1995). The Latin binomials given for the derivative fungi describe imperfect fruit bodies generated when the various mycelia were allowed to grow out. Although derived from the fruit body of Cordyceps sinensis, they are characteristically enough from the parent fungus, to be taxonomically separate; hence the term fungi imperfecti (Alexopoulos, 1962)

**TABLE 3. SEVEN CLASSES OF CHEMICAL CONSTITUENTS OF NATURAL CORDYCEPS**

**1.** Proteins, peptides, all essential amino acids, and polyamines. In addition to all the essential amino acids, Cordyceps contains uncommon cyclic dipeptides including cyclo-(Gly-Pro), cyclo-(Leu-Pro), cyclo-(Val-Pro), cyclo-(Ala-Leu), cyclo-(Ala-Val), and cyclo-(Thr-Leu). Small amounts of polyamines, including 1,3-diamino propane, cadaverine, spermidine, spermine, and putrescine, have been identified.

**2.** Saccharides and sugar derivatives (eg, d-mannitol) were identified and their pharmacological activity has been reported. A group of interesting oligosaccharides and polysaccharides (Cs-l) isolated from natural Cordyceps stimulate macrophage function, and promote lymphocyte transformation. A bioactive 23-kd-protein-bound polysaccharide was shown to consist mainly of mannose and galactose in a ratio of 3 to 5, and protein.

**3.** Sterols, including ergosterol, Delta-3 ergosterol, ergosterol peroxide,/3-sitosterol, daucosterol, and campesterol.

**4.** Eleven nucleoside compounds have been found in natural Cordyceps. The major nucleosides in C. sinensis include adenine, uracil, uridine, guanosine, thymidine, and deoxyuridine.

**5.** Fatty, acids and other organic acids. Twenty-eight saturated and unsaturated fatty acids and their derivatives have been isolated from C. sinensis. Polar compounds of natural Cordyceps extracts and Cs-4 include many compounds of hydrocarbons, alcohol, and aldehyde.

**6.** Vitamins, including vitamins Bi, B2, B12, E, and K.

**7.** inorganics, including K, Na, Ca, Mg, Fe, Cu, Mn, Zn, Pi, Se, Al, Si, Ni, Sr, Ti, Cr, Ga, V, and Zr.

***Data from Guo, 1986; Huang et al., 1991; Tao, 1995; Xia et al., 1985; Xu, 1992; Yue et al., 1995; Zhu and Xinjingsheng, 1993.***

Table 3 lists seven classes of chemical constituents found in natural *Cordyceps sinensis* and its mycelial fermentation products (Guo, 1986; Huang et al., 1991; Tao, lt295; Xia et al., 1985; Xu, 1992; Yue et al., 1995: Zhu, 1993). Pharmacologically active components of *Cordyceps sinensis* are still incompletely understood. Cordycepin and cordycepic acid were identified initially in Cordyceps militaris by Cunning- ham et al. (1951) and considered as the active components Later, scientists confirmed that cordycepic acid was in fact d-mannitol. As for cordycepin (3'-deoxyadenosine), its existence in C. sinensis has long been controversial. Although many laboratories failed to confirm its presence in this species, a recent study reported characterization of cordycepin and 2'-deoxyadenosine in an extract preparation of *C. sinensis* by use of nuclear magnetic resonance (NMR) and infrared spectroscopy (IR) techniques (Chen and Chu, 1996). In addition, other components, such as adenosine, saccharides, and minor elements, were for many years believed to probably play certain roles in the pharmacology of C. sinensis. In TCM, Cordyceps has been used to treat a wide range of conditions, including respira-ton', renal, liver, and cardiovascular diseases, hyposexuality, and hyperlipidemia (Table 1). Cordyceps has also been used to modulate the immune system and as an adjuvant in cancer therapy. Yet only in comparatively recent times have the medicinal effects of Cordyceps been tested in controlled clinical trials, predominantly in China. In reviewing the results of these studies, where appropriate, we have included animal studies that assist in elucidating the mechanisms of activity involved.

## Improvement of Physical Performance and Quality of Life

The preparation and use of Cordyceps as a tonic beverage, although centuries old, was only given greater attention during the last 20 years in China. The recent success of Chinese runners on a special Cordyceps-containing diet brought greater scientific attention to bear on the potential of the mycelia from Cs-4 to improve physical performance and quality of life. The question researchers are now attempting to answer is whether the putatively enhanced physical endurance attributed to Cordyceps can be supported on a strictly scientific basis.

Preclinical animal studies. The effects of Cordyceps extracts on the energy state of mouse liver were examined using in vivo serial 3]p NMR spectroscopy. After mice were given water extracts of Cs-4 (0.2 or 0.4 g/kg) orally for 7 days, the ratio of adenosine triphosphate (ATP): inorganic phosphate (Pi) in the liver was significantly increased by an average of 45% to 55%, as compared with the placebo control group (both $p < 0.001$ ) (Xu CF, Bao TI', He CH, Zhu JS, Chang J, manuscript in preparation). The elevated ATP:Pi ratios returned to the baseline levels 7 days after Cs-4 treatment was discontinued. Similarly, during a 3-week intra- gastric treatment of mice with water extracts of another mycelial fermentation product, SMIH8819 (0.2 g/kg per day), there was a consistent increase in the ratio of ATP:Pi in the liver (Manabe et al., 1996). This increase, observed after 1 week of treatment, was maintained throughout the study and was significantly greater than that of control groups.

In addition to the promotion of higher bioenergy levels by Cordyceps, researchers examined oxygen consumption by mice and their ability to survive after Cs-4 therapy in a hypoxic environment, to elucidate the effects of Cs-4 on oxygen utilization efficiency (Lou et al.,1986). Under conditions of stimulation of oxygen consumption by a subcutaneous injection of isoprenaline (300 ,ug/kg), Cs-4 extract (equivalent to crude Cs- 4, 5 g/kg, J.p., or 10g/kg, i.g.) significantly reduced oxygen consumption by the mice by 41% to 49% within 10 minutes and by 30% to 36% in the second 10 minutes, as compared with controls (all $p <0.001$) (Lou et al., 1986). In a low-oxygen environment, the mice lived 2 to 3 times longer after the Cs-4 treatment (all $p < 0.001$). The Cs-4- induced reduction of oxygen consumption and the prolonged survival of treated animals in a hypoxic environment indicated a more efficient use of oxygen to support essential physiological activities of organs/tissues and greater tolerance to hypoxia-induced acidosis than that of the controls.

A more vigorous study was conducted using an in vivo mouse model of epinephrine- induced acute pulmonary edema, which causes systemic anoxia, acidosis, and death (Wan and Zhang, 1985). It was noted that mice treated with Cs-4 (6 g/kg, J.g.) had a significantly greater survival rate: 20% mortality at 30 min- utes after epinephrine treatment compared with 80% mortality in the control group ($p =0.011$); 60% mortality at 60 and 90 minutes after epinephrine treatment compared with 100% mortality in the control group ($p = 0.043$).

These results suggest that natural Cordyceps and its mycelial fermentation products may improve bioenergetic status by improving an internal balance mechanism by which test animals are able to make more efficient utilization of oxygen under economy of energy consumption. This effect may allow animals to manage efficiently inadequate oxygen supply and a basic energy requirement for essential physiological activities, and to promote greater tolerance to hypoxia-induced acidosis than controls. Whether these properties may to some extent account for the apparent overall enhancement of physical capability and endurance and antifatigue effects found in humans using natural Cordyceps, or its fermentation products as a dietary supplement, is currently the focus of ongoing multidisciplinary research at various centers in China.

**Clinical studies:** Placebo-controlled clinical studies examined the effects of Cs-4 therapy in elderly patients with fatigue and other senescence-related symptoms (Cao and Wen, 1993; Zhang et al., 1995). Compared with no improvement in symptoms in the placebo-treated patients, most of the Cs-4-treated patients reported overall clinical improvement (Zhang et al., 1995). The subjective improvements included alleviation of fatigue, cold intolerance, dizziness, frequent nocturia, tinnitus, hyposexuality, and amnesia (Table 4).

**TABLE 4. CLINICAL EFFECTS OF Cs-4 ON SENESCENCE**

| Symptom | Cs-4 | | Placebo | | |
|---|---|---|---|---|---|
| | n | improved | n | improved | p value |
| Intolerance to cold | 28 | 89% | 20 | 5% | <0.001 |
| Fatigue | 26 | 92% | 27 | 14% | <0.001 |
| Dizziness | 24 | 83% | 23 | 26% | <0.001 |
| Tinnitus | 14 | 79% | 15 | 26% | 0.001 |
| Frequent nocturia | 32 | 59% | 29 | 28% | 0.004 |
| Hyposexuality | 29 | 14% | 30 | 0% | 0.050 |

| | | | | | |
|---|---|---|---|---|---|
| Amnesia | 31 | 26% | 30 | 0% | 0.003 |

Elderly people with symptoms of senescence were enrolled in a double-blind trial and treated with either Cs-4 or placebo (3 g/day) for 3 months. Note: n = number of patients with the symptom prior to the treatment. Results are expressed as percentage of patients who experienced clinical improvement. Data are adapted from Zhang et al. (1995).

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**Covers effects on Heart, Kidney, Liver, Endocrine and Sexual Performance**

Another active-herb (seed oil of mujingyou, Vitex negundo var.heterophylla) - controlled clinical study found that after receiving Cs-4 treatment for 1 month, patients with respiratory diseases felt physically stronger; some of them were able to jog for 20 meters (Institute of Materia Medica, Beijing, China, unpublished report). The Cs-4 treatment appeared to be highly efficacious with a total effective rate of 82.9%, as compared with 40.2% for the active control group ($p < 0.01$).

A study on the long-term use of Cs-4 in combination with standard therapy in patients with chronic heart failure was the subject of a study in China in patients on digoxin, hydrochlorothiazide, isosorbide dinitrate, furosemide, lanatoside, dopamine, and dobutamine (Chen, 1995). Long term administration of Cs-4 as an adjuvant treatment in patients with congestive heart failure gave rise to significantly greater improvements in quality of life than reportedby disease- and age-matched control patients who received only standard drug treatments for congestive heart failure. Quality of life parameters included improvements of general physical condition, mental health, sexual drive, and cardiac function (Table 5).

The enhancement of physical performance and amelioration of quality of life in response to Cs-4 treatment may be attributed to the improvement of energy states with greater efficiency of oxygen utilization described earlier, as well as to the function improvement in oxygen scavenging and in pulmonary, cardiovascular, and other systems, as detailed below, or in part II of this review.

**TABLE 5. IMPROVEMENT OF QUALITY OF LIFE OF PATIENTS WITH CHRONIC HEART FAILURE IN RESPONSE TO LONG-TERM CS.-4 ADJUVANT TREATMENT**

| | Control | Cs-4 | p value |
|---|---|---|---|
| **N** | 30 | 34 | |
| **Age (years)** | 59 ± 5 | 62 ± 7 | n.s. |
| **Shortness of breath / Fatigue index** | 1.00± 0.08 | 1.27± 0.13 | <0.01 |
| **General physical condition** | 1.00± 0.37 | 1.47± 0.40 | <0.05 |
| **Emotional-phychological condition** | 1.00± 0.03 | 1.25± 0.05 | <0.05 |

| | | | |
|---|---|---|---|
| **Sexual drive** | 1.00± 0.03 | 1.65± 0.03 | <0.001 |

Patients with chronic heart failure were treated with Cs-4 (3-4 g/day) for 26 ± 3 months, in addition to standard drug treatments for congestive heart failure. Data are adapted from Chen (1995) and are expressed as fractions of mean values observed for controls who received only standard therapies without Cs4 adjuvant treatment. Shortness of breath/fatigue index was assessed according to Yale grading system; general physical condition according to Feistein method; emotional-psychological condition according to Croog method; and sexuality of patients was based on a modified Kong questionnaire. note: n.s., not significant compared with pretreatment values.

**Anti senescence and oxygen-free radical scavenging activity**

The use of natural Cordyceps to ameliorate conditions associated with aging and senescence is centuries old. Yet scientific research of its potential in geriatrics has only recently been initiated. There is evidence to show that during aging in humans and animals, a considerable accumulation of an excess of oxygen-free radicals occurs, which results in oxidative damage to cells and their intracellular organelles, including age- and illness-associated damage to the energy-producing mitochondria. As one mechanism, an aging- or disease-related dramatic reduction in the oxygen free radical-scavenging activity of superoxide dismutase (SOD) is believed to be responsible for excessive cellular oxidative damage. The anti senescence effects of Cordyceps in relation to an ability to activate SOD and scavenge oxygen free radicals were studied in humans and animals.

In placebo-controlled clinical trials (Cao and Wen, 1993; Zhang et al., 1995), Cs-4 was administered orally to elderly patients with asthenia. In association with the majority showing subjective improvement (as shown in Table 4), there was a concomitant significant increase in red blood cell (RBC) SOD activity in the Cs-4-treated patients (Table 6), which was significantly better than that of the placebo group. Associated with the increase of SOD, concentrations of plasma malondialdehyde (MDA, a measure of lipoperoxide, an oxygen free-radical species) were significantly decreased in Cs-4-treated elderly patients, whereas there was no significant change in the control group. As also demonstrated in this study (Table 6), even with age-associated low pretreatment SOD activity and high MDA concentrations in the elderly patients, treatment with Cs-4 increased SOD activity to levels significantly higher than in young adult controls and reduced plasma MDA content to levels comparable to those of the young adults (Zhang et al., 1995).

**TABLE 6. INCREASES IN SOD ACTIVITY AND DECREASE IN PLASMA MDA (A MEASURE OF LIPOPEROXIDE) IN ELDERLY PEOPLE AFTER CS-4 TREATMENT**

| | | SOD Activity | | | MDA Concentration | |
|---|---|---|---|---|---|---|
| | | n | Pretreatment | Posttreatment | Pretreatment | Posttreatment |
| | **Cs-4** | 33 | 0.93 ± 0.15 | 1.07 ± 0.15* | 1.62 ± 0.31 | 1.08 ± 0.36 |
| **Elderly** | **Placebo** | 26 | 0.87 ± 0.16 | 0.86 ± 0.20 | 1.71 ± 0.41 | 1.73 ± 0.47 |
| | **p value** | | | <0.001 | | <0.001 |
| | | | | | | |
| **Young Control** | | 30 | 1.00 ± 0.13 | | 1.00 ± 0.28 | |

Elderly people (60-84 years old) were treated with either Cs-4 or placebo (3 g/day for 3 months). Data are adapted from Zang et al. (1985), and are expressed as fractions of mean values observed in young adult controls (17-20 years old).
*p < 0.001 compared with pretreatment values.

An increase in SOD activity has been associated with a remarkable clinical improvement in elderly patients in two open-label clinical trials. In the first, after being treated with Cs-4, elderly patients with chronic obstructive pulmonary disease (COPD) showed a marked improvement in cough, phlegm, appetite, vitality, and pulmonary, symptoms (Wang, 1995).Compared with pretreatment baselines, concomitantly, there was a significant increase in SOD activity (Table 7). In the other trial, patients with chronic renal dysfunction were treated with Cs-4 for 1 month (Jiang and Gao, 1995). After treatment, there was a significant increase in total SOD activity (Table 7) compared to pre- treatment levels. In addition, lipoperoxide (LPO) concentrations were significantly de- creased. These findings suggested that Cs-4 enhanced the body's ability to scavenge oxygen-free radicals in different disease conditions.

Natural Cordyceps and mycelial fermentation products of Cordyceps have both shown significant antioxidation effects. For instance, a significant increase in SOD activity and decrease in LPO concentration were found in liver homogenates after treatment of mice with either natural Cordyceps or fermentation Cn80- 2 (Paecilomyces sinensis) product (1.3 g/mL) for 14 days, as compared with placebo controls (p < 0.05-0.01) (Liu et al., 1991).

In addition to the free radical hypothesis, another concern in relation to the aging process is catalytic increases in monoamine oxidase-B (MAO-B), which particularly occurs after age 45 (Sparks et al., 1991). This enzyme resides on the membrane of mitochondria. Increases in the catalytic function of MAO-B that occur with aging and in some aging-related mental diseases result in an altered metabolism of dopamine and other monoamine neurotransmitters. Researchers suspect that inhibition of MAO-B activity by Cordyceps may benefit the elderly by increasing brain concentrations of numerous amines. When tested in brain homogenates of mice or rats in vitro, MAO-B activity was significantly inhibited (She, 1991). These results were found after treating brain homogenates of rats or mice with extract of Cs-4 or other mycelial fermentation products at a ratio of 1:1 0 (Table 8).

**Table 7. INCREASES IN SOD ACTIVITY IN ELDERLY COPD PATIENTS AND RENAL DYSFUNCTION PATIENTS ON Cs-4 TREATMENT**

| | | SOD Activity | | | |
|---|---|---|---|---|---|
| **Disease** | **N** | **Pretreatment** | **Posttreatment** | **p value** | **Reference** |
| **COPD** | 35 | 1.00 ± 0.34 | 1.40 ± 0.42 | <0.001 | Wang (1995) |
| **Renal Dysfunction** | 37 | 1.00 ± 0.39 | 1.51 ± 0.34 | <0.001 | Jiang & Gao (1995) |

Patients with either COPD (56 to 79 years of age) or renal dysfunction were treated with Cs-4 : COPD patients: 3 g day for 3 weeks; renal dysfunction patients : 5g/day for 4 weeks. Results are expressed as fractions of mean pretreatment values. Data are adapted from Wang (1995) and Jiang and Gao (1995)

**TABLE 8. IN VITRO CATALYTIC INHIBITION OF MONOAMINE OXIDASE B (MAO-B) IN BRAIN HOMOGENATES AFTER INCUBATION WITH CORDYCEPS PREPERATIONS**

| | **MAO-B Activity in Rat Brain** | **p value vs. control** | **MAO-B Activity in mouse brain** | **p value vs. control** |
|---|---|---|---|---|
| **Control** | 1.00 ± 0.02 | | 1.00 ± 0.02 | |
| **Cs-4** | 0.54 ± 0.002 | <0.01 | 0.58 ± 0.01 | <0.01 |
| **MF-Cs1** | 0.45 ± 0.02 | <0.01 | 0.43 ± 0.02 | <0.01 |
| **MF-Cs2** | 0.59 ± 0.02 | <0.01 | 0.59 ± 0.02 | <0.01 |

MOA-B catalytic activity was measured with brain homogenates prepared from rats and mice, and incubated with either a placebo or an extract of Cordyceps Mycelial fermentation product in 37 deg. C for 20 minutes. MF-Cs1 and MF-Cs2 were different Cordyceps Mycelial fermentation products from Tatong Liqun Pharmaceuticals, Shanxi, China and Hangzhou Second Pharmaceuticals, Zhejang, China (mycelial strain not stated). Data are adapted from She (1991) and are expressed as fractions of mean values for controls.

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**Effects on sexual functions and endocrine systems**

In the practice of TCM, Cordyceps has long been used to treat male impotence and other types of sexual dysfunction. Recently, the libidinal effects of Cordyceps were examined in the clinic and in animal studies. Animal studies demonstrated that Cs-4 induces sex steroid like effects (Wan et al., 1988). In mice coadministered hydrocortisone (step-incrementa from 30 to 50 mg/kg, i.m.) and Cs-4 (3 g/kg, p.o.) for 15 days, the loss of body weight and atrophy of adrenals and thymus found in un- treated controls was not sustained. In castrated mice, an increase in the weight of the seminal vesicles and preputial glands was measured after Cs-4 treatment (3 g/kg). In the same study, the weight of the preputial glands and testes was increased more than

90% in normal pre- mature male mice (both $p < 0.01$), while in pre- mature female mice, a 6-day Cs-4 treatment (3 g/kg, i.g.) caused an increase in the weight of uterine (+43%) and adrenal tissues (+18%) ($p < 0.01$ and <0.001). The male hormone-like effects of natural Cordyceps were also tested in mice that had undergone bilateral orchiectomy. After treatment with natural Cordyceps (5 g/kg, p.o.) for 7 days, seminal vesicle weight in mice was significantly greater (+41%) than that of age and weight-matched controls ($p < 0.02$) (Wang and Zhao, 1987). After a 3-month treatment with Cs-B414 (10 g/kg, p.o.) (a mycelial extract of Cordyceps, strain not stated), the average weight of rabbit testes (relative to body weight, n -- 8) was significantly 30% greater than that of controls ($p < 0.02$) (Huang et al., 1987). Further analysis of sperm counts showed an average number higher (threefold) than that of controls ($p < 0.05$), and microscopic examinations of seminiferous epithelia revealed normal structure in the treated rabbits. These results suggested that Cordyceps mycelial extracts Cs-B414 might promote spermatogenesis.

The effects of natural Cordyceps on the hypothalamo-pituitary-adrenocortical axis was also examined in a mouse model, which was generated by pretreatment with hydrocortisone (HC; 0.5 mg/day, days 1-10) by intramuscular injection (Huang et al., 1987). The HC pretreatment induced a 58.8% decrease ($p < 0.001$) in the weight of the adrenal glands (7.7 ± 2.1/100 g body weight [BWJ), as compared with the untreated controls (18.7 z 3.2/100 g BW). In one of the experimental groups, mice were injected with natural Cordyceps (2.5 g/kg, J.p., days 2-9) in parallel with the HC treatment. The weight of the adrenal glands was significantly greater (+42%) than those of the HC model group that received placebo ($p < 0.001$). This suggested that Cordyceps had apparently attenuated the effects of HC in adrenal atrophy. These effects on the hypothalamo- pituitary-adrenocortical axis occurred concomitantly with attenuated spleen atrophy and an increased capability of mice to adapt to a cold environment.

In humans, Cs-4 was used in a placebo-controlled clinical trial involving elderly patients reporting decreased libido and other sexually related symptoms (Yang et al., 1995). Cs-4 therapy was associated with a subjective improvement of up to more than double the number of those in the placebo-treated control group (Table 9). This study demonstrated that Cs-4 could benefit both men and women, as detailed in Table 10.

In another double-blind, placebo-controlled clinical trial (Yang et al., 1995), patients who reported decreased sex drive were treated with Cs-4. The total subjected improvement rate in the Cs-4 group was significantly higher than that observed in the placebo control group (Table 9). Moreover, an increase in 24-hour urine 17-keto-steroid in the Cs-4-treated patients was also revealed in this study, while patients in the control group had a much smaller increase (Table 11 ). These results indicated that Cs-4 might affect patients' sexual drive and functions, either via sex hormone systems or by directly acting on the sexual center of the brain and sexual organs, in parallel with effects on the hypothalamo-pituitary-adrenocortical axis.

Another clinical trial involved 189 patients who reported decreased sex drive (Wan et al., 1988). After Cs-4 treatment, over half of the subjects in the Cs-4 group reported improvement, which was significantly greater than that reported by the placebo control group (Table 9). Also reported in this study, Cs-4 treatment of 28 impotent male patients (not included in Table 9) led to an improvement in 64.3% of patients (p < 0.001). In a separate open-label trial involving 22 male patients with impotence, after Cs-4 treatment more than one-third were capable of sexual intercourse and more than half experienced clinical improvement to some extent (Table 12) (Guo, 1986). After Cs-4 treatment in another trial, the average sperm count greatly increased (+33% on average) from pretreatment levels, which was consistent with that found in normal rabbits (Huang et al., 1987). In addition, the average incidence of malformed spermatozoa was reduced and the survival rate of spermatozoa increased. It was suggested that the beneficial effects of Cs-4 might be due in part to the fact that it is rich in amino acids, vitamins, and trace elements such as zinc, which are essential for sperm survival (Guo, 1986).

**TABLE 9. CLINICAL IMPROVEMENT OF SEXUAL FUNCTIONS IN PATIENTS WITH VARIOUS KINDS OF HYPOSEXUALITY**

| | Institute of Materia Medica* | | Yang et al. (1995) | | Wan et al. (1988) | |
|---|---|---|---|---|---|---|
| | n | Improved | n | Improved | n | Improved |
| **Placebo** | 60 | 24.0% | 97 | 23.6% | 97 | 23.7% |
| **Cs-4** | 144 | 65.3% | 159 | 64.1% | 189 | 66.1% |
| **p value** | | <0.001 | | <0.001 | | <0.001 |

In double blind studies, patients with hyposexuality were treated with either a placebo or Cs-4 (3 grams/day) for 40 days.
Data are adapted from the references indicated.
*Institute of Materia Medica, Bejing, China, Unpublished report

**TABLE 10. IMPROVEMENTS OF SEXUAL FUNCTION IN BOTH MALE AND FEMALE ELDERLY SUBJECTS AFTER Cs-4 TREATMENT**

| Male | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Impotent | | | Prospermia | | | Emission | | | Hypolibidinal | | |
| | | Improved | | | Improved | | | Improved | | | Improved | |
| | n | n | (%) | n | n | (%) | n | n | (%) | n | n | (%) |
| **Placebo** | 90 | 21 | (23%) | 13 | 4 | (31%) | 3 | 0 | (0%) | 5 | 0 | (0%) |
| **Cs-4** | 133 | 88 | (66%) | 22 | 10 | (46%) | 6 | 4 | (67%) | 6 | 4 | (67%) |
| **p value** | | <0.001 | | | <0.037 | | | <0.034 | | | <0.004 | |

| Female |
|---|

| | Hypolibidinal | | | Menoxenia | | | Hypoleukorrhagia | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Improved | | | Improved | | | Improved | |
| | n | n | (%) | n | n | (%) | n | n | (%) |
| **Placebo** | 4 | 0 | (0%) | 1 | 0 | (0%) | 1 | 0 | (0%) |
| **Cs-4** | 7 | 6 | (86%) | 2 | 2 | (100%) | 6 | 6 | (100%) |
| **p value** | | | <0.001 | | | | | | |

Patients with hyposexuality were treated with either a placebo or Cs-4 (3 g/day) for 40 days in a double blind study.

Data are adapted from an unpublished report by the Institute of Materia Medica, Bejing, China.

**TABLE 11. Increase in 17-Hydroxycorticosteroid (17-OHCS) and 17-Ketosteroid (17-KS) in 24-hour urine in patients with Hyposexuality on CS-4 Therapy**

| | | 17-OHCS (24 hour urine) | | 17-KS (24 hour urine) | |
|---|---|---|---|---|---|
| | n | pretreatment | postreatment | pretreatment | postreatment |
| **Placebo** | 51 | 1.00+-0.11 | 1.03+-0.05 | 1.00+-0.29 | 1.03+-0.23 |
| **Cs-4** | 71 | 0.99+-0.05 | 1.21+-0.17 | 1.15+-0.18 | 1.23+-0.15 |
| **p value** | | | <0.001 | | <0.001 |

In a double blind study, patients with hyposexuality were treated either with placebo or Cs-4 (3 grams/day) for 40 days. Data are adapted from Yang et al. (1995) and are expressed as fractions of mean pretreatment values for placebo control patients.

**TABLE 12. QUANTITATIVE AND QUALITATIVE IMPROVEMENT OF SPERMATOZOA IN 22 MALE PATIENTS WITH SEXUAL DYSFUNCTION**

| | | SPERMS | | |
|---|---|---|---|---|
| | Capable of Sexual Life | Count (Millions/ml) | Incidence of Malformation | Survival Rate |
| **Pretreatment** | 0% | 99 | 70% | 29% |
| **Postreatment** | 37% | 132 | 50% | 52% |
| **% Change** | | +33% | -29% | +79% |

Patients with male impotence were treated with Cs-4 (3 g/day) for 8 weeks. Data are adapted from Guo (1986).

## Effects on blood lipid metabolism and atherosclerosis

Clinicians in China have recommended Cs- 4 for the treatment of refractory hyperlipidemia (Zhang ZJ, Jiangxi Medical College The Second Affiliated Hospital, unpublished report). Studies have suggested that natural Cordyceps and its mycelial fermentation products can regulate the metabolism of blood lipids, control hyperlipidemia, and act against the formation of atherosclerosis.

Preclinical animal studies on the hypolipidemic effects of Cordyceps. When normal rats were treated with Cs-4 for 1 week, serum total cholesterol (TC) and triglycerides (TG) were significantly reduced (upper panel, Table 13) (Xu and Zhang, 1985). Low-density lipoprotein-cholesterol (LDL-c) and very low-density lipoprotein-cholesterol (vLDL-c) were decreased, while high-density lipoprotein cholesterol (HDL-c) was increased. As a result, the ratio of HDL-c:TC showed a very significant increase.

Under experimental conditions of stress in rats, intragastric perfusion of Cs-4 produced significant decreases in TC, TG, and LDL-c (middle panel, Table 13) and an increase in the ratio of HDL-c:TC (Xu and Zhang, 1985). In rats fed a fat-rich diet, Cs-4 reduced serum TC, TG, LDL-c, and vLDL-c (lower panel, Table 13). In addition, Cs-4 treatment was associated with an increase in HDL-c and an increased ratio of HDL-c:TC, when compared with controls. In addition to reducing serum TC and (BETA) lipoprotein, Cs-4 and its concentrated product, CsB- 851, can also interrupt the formation of athero- matous plaque in the aorta and inhibit thrombosis on the surface of experimentally injured endothelia of arteries (Bao, 1995; Yue et al., 1995).

The mechanism of cholesterol-lowering effects of Cs-4 has also been studied. When the concentrated product of Cs-4, CsB-851 (200 mg/kg, s.c.) was tested in mice, 14C incorporation into newly synthesized cholesterol was significantly reduced by about half (Li et al., 1992). This indicated an in vivo inhibition of endogenous cholesterol biosynthesis. It was further demonstrated in this study that CsB- 851 (800 mg/kg per day, for 3 days) did not change fecal discharge of 3H-neutral cholesterol given by mouth, suggesting that there were no changes in the absorption and excretion of cholesterol via the gastrointestinal tract.

To elucidate the mechanism of the TG-lowering effects of Cs-4, investigators pretreated rats intragastrically with Cs-4 and found a 27% decrease of plasma triglycerides and an 8.7% increase of plasma free fatty acids (Table 14) (Xu and Zhang, 1985). After activation of lipoprotein lipase (LPL) by heparinization (heparin injection), the difference in triglycerides between the experimental and placebo control groups was eliminated. Because LPL residing on the endothelia of the blood vessels can be released by heparin and catalyzes the hydrolysis of triglycerides to yield glycerol and free fatty acids, these findings suggest that the triglyceride-reducing effect found in the Cs-4 group prior to the heparinization could be due, at least in part, to a Cs-4-mediated activation of LPL. A 45-kd polysaccharide, CS-F30 was purified from a fermentation product of Cordyceps and tested in animals (Kiho et al., 1996) This Polysaccharide is composed of galactose, glucose, and mannose at a molar ratio of 62:28:10. In addition to dramatic reductions of blood glucose, serum TG was significantly reduced in normal mice at 3 (- 26%) and 6 hours -.28%) after administration of CS-F30 (50 mg/kg, i.p.), as compared with controls (p < ).01). Three hours after the polysaccharide treatment, TC was lowered by 16% in normal nice, and 23% in streptozotocin (STZ)-induced diabetic mice, as compared to baseline (both < 0.01). These results suggest that in conjunction with other natural bioactive components in Cordyceps, the 45-kd polysaccharide may play an important role in reducing blood lipids and glucose.

**TABLE 13. Changes in Blood Lipid in Rats**
**After Receiving a 7-Day Cs-4 Treatment**

| | n | TC | TG | HDL-c | LDL-c v | LDL-c |
|---|---|---|---|---|---|---|
| **Placebo** | 10 | 1.00+-0.05 | 1.00+-0.04 | 1.00+-0.08 | 1.00+-0.06 | 1.00+-0.04 |
| **Cs-4** | 10 | 0.64+-0.05 | 0.65+-0.04 | 1.35+-0.04 | 0.44+-0.04 | 0.65+-0.04 |
| **p value** | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| | | | | | | |
| **Placebo** | 8 | 1.00+-0.05 | 1.00+-0.11 | | 1.00+-0.07 | |
| **Cs-4** | 8 | 0.68+-0.03 | 0.66+-0.03 | | 0.52+-0.06 | |
| **p value** | | <0.001 | <0.001 | | <0.001 | |
| | | | | | | |
| **Placebo** | 12 | 1.00+-0.10 | 1.00+-0.14 | 1.00+-0.08 | 1.00+-0.01 | 1.00+-0.14 |
| **Cs-4** | 10 | 0.54+-0.06 | 0.33+-0.04 | 1.59+-0.07 | 0.46+-0.01 | 0.33+-0.04 |
| **p value** | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Normal rats (upper panel) or rats under experimental stress conditions (middle panel) were treated either with a placebo or Cs-4 (5 grams/day) for 7 days, or rats were fed a fat-rich diet (4% cholesterol, 1% cholic acid, 10% lard) for 30 days (lower panel) in combination with either placebo or Cs-4 (5 grams/day); they were also given noradrenalin (20 mg/day) daily, 6-7 hours after placebo or Cs-4 treatment. Data are adapted from Xu and Zhang (1984) and are expressed as fractions of mean pretreatment values for placebo controls in each experiment.

**Clinical use of natural Cordyceps and its fermentation products**
**in the treatment of hyperlipidemia.**

In a double-blind, placebo-controlled clinical trial in 273 patients with hyperlipidemia, a significant reduction of TG was found with controls after only 1 month of treatment with Cs-4 (Table 15) (Shao et al., 1990). After a 2-month treatment, a significant reduction in TC and a significant increase in beneficial HDL-c were found. Overall, well over half of the patients on Cs-4 therapy displayed greater than 10% decrease in TC, while half showed greater than 20% decreases in TG and 76% of patients had greater than 10% increase in HDL-c.

In a randomized clinical trial, patients were treated with Cs-4 while a control group received an herb, yuejiancao jouwan (an Oenolhera preparation) (Quin et al., 1995). In the Cs-4 treatment group, serum TC and TG were significantly decreased from baseline, and HDL-c was significantly increased (Table 15).

In a clinical study with 20 patients suffering from coronary heart disease, there was a significant reduction of both TC and TG after Cs- 4 treatment, and (BETA) lipoprotein was significantly decreased (Table 15) (Che and Lin, 1996). The viscosity of plasma and whole blood was significantly decreased (both $p < 0.01$). Both associated electrocardiographic improvement and subjective clinical improvement were evident.

In an open-label trial in 32 elderly patients with hyperlipidemia treated with Cs-4, there was a significantly decreased serum TC and TG compared with the baseline and a significantly increased HDL-c (Table 15) (Tong, 1995). Serum TC was lowered by more than 10% in 55.5% of the subjects and TG by more than 20% in 57.5%, while HDL-c was increased by more than 4 mg/dL in 70.6% of the patients.

Overall, the Cs-4 treatment was associated with a significant reduction of cholesterol and triglycerides and an increase in HDL-c. However, the variations in the magnitude of the response to Cordyceps demonstrated in these trials may be related to different pretreatment baselines of cholesterol and triglycerides for the trial subject populations. Added to the effects of Cs-4 in reducing oxidative stress resulting in lipid oxidation by increasing the scavenging of oxygen free radicals (lipoperoxide) as shown in Tables 6 and 7 (Cao and Wen, 1993; Jiang and Gao, 1995; Liu et al., 1991; Wang, 1995; Zhang et al., 1995), and its ability to reduce blood viscosity in clinical studies (Che and Lin, 1996), the changes observed in blood lipids indicate that Cs-4 may well produce beneficial effects in the treatment and prevention of atherosclerosis and subsequent cardiovascular and cerebrovascular diseases with fewer side effects.

**TABLE 14. Changes in Plasma Triglycerides and Free Fatty Acids in Rats After Recieving a 7 Day Cs-4 Treatment**

| | n | Preheparinization | Postheparinization | Difference (pre minus post) |
|---|---|---|---|---|
| **Triglycerides** | mg/dL | | | |
| **Placebo** | 10 | 1.00+-0.07 | 0.37+-0.03 | 0.63+-0.07 |
| **Cs-4** | 10 | 0.73+-0.08 | 0.32+-0.03 | 0.41+-0.09 |
| **p value** | | <0.001 | >0.05 | <0.01 |
| | | | | |
| **Free Fatty Acids** | umol/L | | | |
| **Placebo** | 10 | 1.00+-0.08 | 2.46+-0.21 | 1.46+-0.20 |

| | | | | |
|---|---|---|---|---|
| **Cs-4** | 10 | 1.08+-0.06 | 3.79+-0.27 | 2.70+-0.26 |
| **p value** | | >0.05 | <0.001 | <0.001 |

Normal rats were treated p.o. with either placebo or Cs-4 (5 grams/day) for 7 days.they were anesthetized and catheterized arterially. Blood samples were collected 2 minutes before and after heparin injection (0.4 mg/kg) and analyzed for plasma triglycerides and free fatty acid concentrations. Data are adapted from Xu and Zhang (1984) and are expressed as fractions of mean pre heparinization values for placebo controls.

**TABLE 15. Percentage Changes in Blood Lipids in Patients with Hyperlipidimia After Cs-4 Treatment**

| Reference | n | Cs-4 dose | (month) | TC | TG | HDL-c | b-lipoprotein |
|---|---|---|---|---|---|---|---|
| **Shao et al (1990)** | 273 | 3 g/day | 2 | -17.5% | -9.2% | +27.2% | |
| **Qin et al (1995)** | 62 | 3 g/day | 1 | -16% | -26% | +30% | |
| **Che and Lin (1996)** | 20 | 3 g/day | 2 | -21% | -21% | | -12% |
| **Tong (1990)** | 32 | 3 g/day | 2 | -20.5% | -20.5% | +26.7% | |

Patients with Hyperlipidemia were treated with Cs-4 (dose and length of treatment as indicated). data are adapted from the references indicated and are expressed as percentage change from pretreatment values. Note:"-" means decrease; "+" means increase.

***NOTE:** ***These claims have not been evaluated by the FDA. Our products are not intended to diagnose, treat, cure or prevent any disease. Health decisions are much too important to be made without the advice of a Doctor or other Healthcare Practitioner. We invite and encourage you to share this information with your doctor. We are happy to share all of our research materials with any doctor who asks.***