THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 4, Number 4, 1998, pp. 429–457
Mary Ann Liebert, Inc.

The Scientific Rediscovery of a Precious Ancient Chinese Herbal Regimen: *Cordyceps sinensis* Part II

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ABSTRACT

***Cordyceps sinensis* (Berk.) Sacc. is a time-honored tonic food and herbal medicine in China, where recent research has shown that many of its traditional uses may be viewed from the basis of pharmacological activities. The ongoing exploration of *C. sinensis* in its wild form and cultured, fermented mycelial products derived from it, are reviewed from English and Chinese literature. Part II concludes the series with a review of *C. sinensis* in preclinical *in vitro* and *in vivo* studies, and open-label and double-blinded clinical trials on the respiratory, renal, hepatic, cardiovascular, immunologic, and nervous systems, and its effects on cancer, glucose metabolism, inflammatory conditions, and toxicological studies. In Part I, which appeared in the Fall 1998 issue of this journal (4(3):289–303), we discussed the effects of *C. sinensis* on antisenescence, endocrine and sexual functions, atherosclerosis, hyperlipidemia, and free radicals.**

EFFECTS ON THE RESPIRATORY SYSTEM

The use of Cordyceps (*Cordyceps sinensis* [Berk.] Sacc.) in the treatment of respiratory diseases is centuries old. Cordyceps has an extensive history of use in the treatment of chronic bronchitis, especially in elderly patients, and of asthma, chronic obstructive pulmonary disease (COPD), tuberculosis, cor pulmonale, and other diseases of the respiratory system. Some of these applications may be related to the ability of Cs-4 to affect tracheal and bronchial functions.

Pre-clinical pharmacology of Cordyceps in the respiratory system

One of the most interesting pharmacological effects of natural Cordyceps and its fermentation products on the respiratory tract involves expectoration and cough, with improved pulmonary functions. In preclinical animal studies (Wan F, Zhang S. Clinical observations of fermented *Cordyceps sinensis* (Cs-4) in antitussive, expectorant, and antathematic effects. Unpublished report, Nanchang, Jianhxi China: Jiangxi Institute of Medical Sciences, pp. 35–39.), Cs-4 extracts (6 g/kg, i.g.) increased in-

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tratracheal secretion (+114% to +197%; $p <$ 0.01 to < 0.001) in rats with a peak during the second hour after Cs-4 treatment, therefore facilitating expectoration. Similar results were found after natural Cordyceps treatment (+141% to +251%; $p < 0.01$ to < 0.001). Along with the increases in trachea secretion volume, Cordyceps also increased dye secretion through the tracheal mucosa. After treatment with natural Cordyceps (3.1 g/kg, p.o.) or other fermented mycelial products of Cordyceps (2.5 g/kg, p.o.), mice were administrated phenol red. Secretion of phenol red was dramatically increased (+66% to +61%) in mice treated with natural Cordyceps and its fermentation product, as compared to placebo controls ($p < 0.05$) (Wang and Zhao, 1987).

In addition to the increase in tracheal secretion, Cordyceps has also been proven to show an antitussive function. For instance, treatment with Cs-4 (5 g/kg, i.g.) was effective against experimental ammonia-induced cough in mice. Cough-latent period was significantly prolonged by about 5 times and cough frequency was decreased by two-thirds in the Cs-4 group, as compared to placebo controls ($p < 0.001$ and < 0.01) (Wan F, Zhang S. Clinical observations of fermented *Cordyceps sinensis* (Cs-4) in antitussive, expectorant, and antathematic effects. Unpublished report, Nanchang, Jianhxi China: Jiangxi Institute of Medical Sciences, pp. 35–39). These effects of Cs-4 were similar to those of codeine at a dose of 60 mg/kg.

It was also demonstrated that Cs-4 plus cultured medium could significantly relax tracheal smooth muscles in trachea isolated from guinea-pigs with histamine-induced spasm (Wan F, Zhang S. Clinical observations of fermented *Cordyceps sinensis* (Cs-4) in antitussive, expectorant, and antathematic effects. Unpublished report, Nanchang, Jianhxi China: Jiangxi Institute of Medical Sciences, pp. 35–39). Length of the histamine-pretreated trachea increased 7.5 times after adding Cs-4 (5 mg/mL) to the medium, as compared to placebo controls ($p < 0.01$). Another study also demonstrated that natural Cordyceps (2.17 g/kg) and Cs-4 (1.74 g/kg) could significantly prolong the latent period (5.44- and 4.75-fold of controls, respectively; both $p < 0.01$) of asthma development induced by acetylcholine in guinea pigs (Wang and Zhao, 1987). Further increases in the latent period (7.58- and 7.25-fold of controls, respectively; both $p < 0.01$) were also seen after guinea pigs received natural Cordyceps (1.08 g/kg) or Cs-4 (0.87 g/kg) treatment in combination with aminophylline (63.5 mg/kg). Similarly, natural Cordyceps and a fermented mycelial product of Cordyceps (SMIH8819) displayed relaxation effects on twitch contractions of the trachea (Tsunoo et al., 1995).

Clinical use of Cordyceps to improve respiratory functions

Several studies have demonstrated an improvement in clinical symptoms of respiratory diseases after the administration of a Cordyceps-containing medication. For example, the vast majority of patients with various respiratory diseases, such as chronic bronchitis, bronchial asthma, or cor pulmonale, reported a significant clincal improvement after Cs-4 treatment (Table 1) (Han, 1995). In another clin-

TABLE 1. SUMMARY OF CLINICAL EFFICACY OF CS-4 IN THE TREATMENT OF RESPIRATORY DISEASES

Reference	*Cs-4 dosage*	*Weeks of treatment*	n	*Clinically improved*	
				n	%
Han (1995)	3 g/day	2 → 12	100	92	92%
Qu et al. (1995)	3 g/day	4	30	26	87%
Zheng and Deng (1995)	3 g/day	4	20	17	85%
Yang (1985)	4.5 g/day	4	27	21	78%
Zheng et al. (1985)	4.5 g/day	4	20	18	90%

Patients with respiratory diseases were treated with Cs-4 (dose and length of treatment indicated). The clinical improvement rates were significantly greater than negative controls (all $p < 0.01$), or as effective as positive controls in different studies (data for controls are not shown).

Data are adapted from the following references: Han, 1995; Qu et al., 1995; Zheng and Deng, 1995; Yang, 1985; Zheng et al., 1985.

FIG. 1. Stromata of *Cordyceps sinensis* (Berk.) Sacc.; photograph by Prof. Su-Yun Zhao. With permission from *National Collection of Chinese Traditional Medicine: Colored Illustrations*, Second edition. People's Health Publications, Beijing, 1996.

ical trial (Qu et al., 1995), Cs-4 treated patients with various respiratory diseases, with or without antibiotics, were as improved as a positive control group treated with a known, effective drug, Bai-Ling capsule (*Swnnematium sinense* Yin et Shen sp. nov.) (Table 1). In other studies, Cs-4 treatment of patients suffering from chronic bronchitis or bronchitis with asthma resulted in very high rates of clinical improvement, versus the representative control groups (Table 1) (Zheng and Deng, 1995; Yang, 1985; Zheng et al., 1985). Improvements in respiratory capacity were also noted in these studies (Table 2) (Zheng et al., 1985).

Combined use in treating cor pulmonale

Cs-4 has also been used in combination with other drugs to treat patients suffering from cor pulmonale, either acute or recurring acutely with first-degree to third-degree heart-lung dysfunction (Lei and Wang, 1995). Addition of Cs-4 to the basic treatment of oxygen inhalation and antibiotics resulted in a highly improved overall rate of therapeutic effect when symptoms, including asthma, cough and expectoration, sleep, emotional-spiritual state, respiratory functions, and heart functions, were assessed (Table 3). This improvement was significantly greater than the overall effective rate reported for the control group, which received basic therapy without Cs-4. The results indicated a greater improvement in quality of life for the patients after administration of Cs-4.

Clinical use in treating cough as an equivalent of asthma

The combined use of Cs-4 (3 g/day for 10 days) with Western medicines (astemizole 10 mg/day and ketotifen 2 mg/day) in the treat-

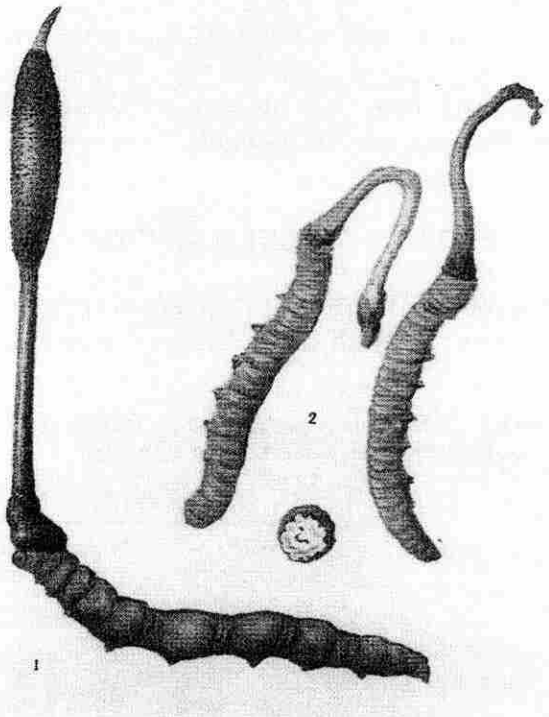

FIG. 2. Natural *Cordyceps sinensis* (Berk.) Sacc. Note: (1) showing the part of protozoon and stroma; (2) showing natural *Cordyceps sinensis* used in Chinese herbal medicine. With permission from *Colored Icones of Chinese Medicine*, Hsien Shui Lo, ed., Guangdong Science and Technology Publications, Guangzhou, 1994, Vol. III.

TABLE 2. CHANGES IN PULMONARY FUNCTIONS IN CHRONIC BRONCHITIS PATIENTS AFTER Cs-4 ADJUVANT TREATMENT

	n	*Difference (post minus pre)*	p *value*
Timed vital capacity	20	300 ± 307	<0.01
Ratio of FEV_1:FEV (%)	20	7.3 ± 6.8	<0.01
Ratio of FEV_3:FEV (%)	20	5.9 ± 1.6	<0.01
Maximum breathing capacity	20	11,022 ± 17,818	<0.05
Maximum breathing capacity (%)	20	8.25 ± 10.1	<0.01

Patients with chronic bronchitis were treated with Cs-4 (3 g/day, 1 month).
FEV_1, forced expiratory volume in the first second; FEV_3 forced expiratory volume in the first 3 seconds.
Data are adapted from Zheng et al. (1985).

ment of patients with cough as an equivalent of asthma was in one study associated with an 81% improvement rate ($n = 32$), which was greater than the 61% rate observed for a control group ($n = 18$) treated with Western medicine alone ($p < 0.05$) (Qiuo and Ma, 1993). In addition, the patients in the Cs-4 group experienced faster relief of their cough symptoms (within 5 days on average) as compared to the control group (9 days). Among the asthmatic patients, the 10-day treatment with Cs-4 resulted in improved ventilation functions: the forced expiratory volume in first-second ($FEV_{1.0}$) was increased by approximately 15% from the pretreatment baseline.

EFFECTS ON THE KIDNEYS

In accord with the most recognized action of Cordyceps in traditional Chinese medicine (TCM), pharmacological studies of the "kidney tonic" tend to bear out this time-honored traditional use. China's physicians have made extensive use of Cordyceps in the treatment of chronic renal diseases, including chronic nephritis, chronic renal dysfunction or failure, chronic pyelonephritis, and nephrotic syndrome. Studies have shown that Cordyceps could improve kidney functions and act against the damage caused by certain nephrotoxic chemicals.

TABLE 3. CLINICAL IMPROVEMENT OF PATIENTS WITH COR PULMONALE BY Cs-4 ADJUVANT TREATMENT

	Clinical improvement			
	With Cs-4		*Without Cs-4*	
	n	%	n	%
Shortness of breath	45	90%	20	67%
Cough and expectoration	46	92%	18	60%
Sleep	48	96%	21	70%
Emotional-spiritual state	46	92%	18	60%
Pulmonary function	48	96%	16	53%
Heart function	46	92%	18	60%
Total effective rate		92.0%		61.5%

Patients with cor pulmonale were treated either with ($n = 50$) or without ($n = 30$) Cs-4 (4.5 g/day) for 30 days.
Data are adapted from Lei and Wang (1995).

Effects on renal functions

Cheng et al. (1992) found that as compared to chronic renal failure (CRF) model controls, natural Cordyceps treatment (0.5 g/kg, for 4 months) greatly decreased the mortality of CRF rats, reduced blood urea nitrogen (BUN; −25%) and serum creatinine (SCr; −56%), and improved anemia (hemoglobin, +13%) (all $p < 0.005$) (Cheng et al., 1992). In addition, natural Cordyceps significantly enhanced the transformation rates of splenic lymphocytes and promoted the rate of production of interleukin-2 (IL-2) receptor (+78%, $p < 0.005$) and expression of IL-2 (+21%, $p < 0.005$) in lymphocytes, suggesting a correlation of the functional improvement of the cell-mediated immune system and a delay in the deterioration of renal functions.

In 30 patients with CRF, treatment with Cs-4 significantly improved renal functions (Chen et al., 1986). SCr was significantly reduced; creatinine clearance (Ccr) increased dramatically; and BUN was significantly reduced (Table 4). In addition, there was a dramatic improvement in anemia after Cs-4 therapy: he-

TABLE 4. IMPROVEMENT OF KIDNEY FUNCTIONS BY Cs-4 IN 30 PATIENTS WITH RENAL FAILURE

	Hemoglobin	*RBC*	*SCr*	*Creatinine clearance*	*BUN*
Pretreatment	1.00	1.00	1.00	1.00	1.00
Post-treatment	1.08	1.07	0.91	1.40	0.81
Difference	+0.08 ± 0.03	+0.08 ± 0.04	−0.09 ± 0.03	+0.40 ± 0.07	−0.19 ± 0.06
p value	<0.02	<0.05	<0.02	<0.001	<0.01

Patients with chronic renal failure were treated with Cs-4 (6 g/day) for 30 days.
RBC, red blood cell count; SCr, serum creatinine; BUN, blood urea nitrogen.
Data are adapted from Chen et al. (1986) and are expressed as fractions of mean pretreatment values.

moglobin and red blood cells (RBC) were increased significantly, while transformation rates of lymphocytes also increased significantly.

In another study, patients with chronic renal dysfunction who received Cs-4 treatment showed very significantly reduced BUN and SCr, along with a very noticeable improvement of symptoms (Table 5) (Jiang and Gao, 1995). In association with reduced renal functions, patients with renal failure or dysfunction often suffer from hypertension, proteinuria, and anemia. A 15% decrease in average arterial blood pressure was observed, while urinary proteins were also decreased dramatically. In addition, catalytic increases in superoxide dismutase (SOD) were demonstrated in the patients after one month of Cs-4 treatment. The increase in total SOD was associated with a marked decrease in serum lipoperoxide, suggesting an increase in the oxygen free radical scavenging capacity to reduce oxidative cellular damage.

Clinical studies have shown that a Cordyceps-induced renal function improvement in patients with renal failure significantly coincided with changes in T-cell subgroups (Table 6) (Guan et al., 1992; Chen et al., 1984). These results suggest a possible correlation of improvement of renal dysfunction by Cordyceps with a modulation of T-cell mediated immune functions.

Protection from kidney toxicity

Renal protective effects of Cordyceps against aminoglycoside antibiotics and cyclosporine A nephrotoxicity were tested both in animals and humans. Cs-4 (0.8 g/kg) was administered to rats for 7 days in combination with gentamicin (160 mg/kg), while a gentamicin control group received an equal volume of water (Zheng et al., 1994). After the treatment, increases in accumulated 24-hour urine N-acetyl-β-D-glucosaminidase (NAG), an index for aminoglycoside antibiotic-induced renal damage, appeared to be significantly attenuated by 61% in the rats receiving Cs-4/gentamicin cotreatment, when compared to the gentamicin-model rats ($p < 0.02$). No significant increase was found in urinary sodium excretion in Cs-4-treated rats compared to normal rats; while gentamicin-model rats showed an average 2.7-fold increase in urine sodium excretion ($p < 0.01$). Notably, apparent regeneration of renal tubular cells was found in the Cs-4-treated rats when examined under a microscope. According to increases in isotope incorporation into cultured renal tubular cells,

TABLE 5. IMPROVEMENT OF KIDNEY FUNCTIONS BY Cs-4 IN 37 PATIENTS WITH RENAL FAILURE

	BUN	*Creatinine*	*Arterial pressure*	*Urinary proteins*	*SOD*	*LPO*
Pretreatment	1.00 ± 0.42	1.00 ± 0.42	1.00 ± 0.13	1.00 ± 0.90	1.00 ± 0.39	1.00 ± 0.37
Post-treatment	0.66 ± 0.31	0.61 ± 0.30	0.85 ± 0.07	0.37 ± 0.30	1.51 ± 0.34	0.65 ± 0.17
p value	<0.001	<0.001	<0.01	<0.01	<0.001	<0.001

Patients with chronic renal failure were treated with Cs-4 (5 g/day) for 1 month.
BUN, blood urea nitrogen; SOD, superoxide dismutase; LPO, lipoperoxide.
Data are adapted from Jiang and Gao (1995) and are expressed as fractions of mean pretreatment values.

TABLE 6. IMPROVEMENT OF KIDNEY FUNCTIONS AND ASSOCIATED CHANGES IN T-CELL SUBGROUPS BY NATURAL CORDYCEPS IN 51 PATIENTS WITH RENAL FAILURE

	BUN	*SCr*	*Hemoglobin*	*OKT_4*	*Ratio of OKT_4/T_8*
Pretreatment	1.00 ± 0.23	1.00 ± 0.50	1.00 ± 0.18	1.00 ± 0.16	1.00 ± 0.24
Post-treatment	0.75 ± 0.31	0.69 ± 0.25	1.18 ± 0.21	1.13 ± 0.14	1.16 ± 0.16
p value	<0.05	<0.05	<0.05	<0.05	<0.05

Patients with chronic renal failure were treated with natural Cordyceps (3–5 g/day) for 10–12 months.
BUN, blood urea nitrogen; SCr, serum creatinine.
Data are adapted from Guan et al. (1992) and are expressed as fractions of mean pretreatment values.

serum prepared from Cs-4-treated rats appeared to produce dramatic stimulatory effects on tubular cell proliferation, as compared to that of the gentamicin control serum ($p < 0.01$). In their conclusion, the authors reported that gentamicin nephrotoxicity appeared to be largely compromised by cotreatment with Cs-4, indicating a nephroprotective effect of Cs-4.

Administration of water extracts of natural Cordyceps protected rats from acute renal damage in proximal tubular cells and accelerated recovery of renal functions. After the rats were treated with kanamycin (250 mg/kg plus dextran, 3 g/kg) to produce an acute renal failure (ARF) model, total mortality of the ARF rats was significantly less in the Cordyceps treatment (10 g/kg) group, as compared to the kanamycin control group ($p < 0.05$) (Zheng et al., 1992). BUN and SCr were significantly lower in the Cordyceps group than in the controls ($p < 0.01$ and < 0.05), and urine osmolarity was higher in the Cordyceps-treated rats (both $p < 0.05$). Microscopic examination in multiple view fields of kidney sections in a double-blind fashion demonstrated that the 5-day natural Cordyceps treatment ameliorated acute damage/death of proximal tubular cells of rats and significantly accelerated the process of recovery. Histological damage of tubular cells, greatly attenuated after the 5-day Cordyceps treatment, was found in association with a significant decrease in lysosomal acid phosphatase activity, as compared to diffuse pathological changes in the controls.

Another ARF animal model was created by treatment of rats with gentamicin (140 mg/kg). The rats were administered gentamicin in combination with either placebo or natural Cordyceps (1 g/day) for 7 days. In association with a significant recovery of BUN, SCr, NAG, and histology, catalytic activity of Na^+-K^+-ATPase nearly doubled in the kidney cortex in the Cordyceps-treated rats compared to controls ($p < 0.01$), indicating a more active cellular sodium pump.

In rats treated with natural Cordyceps (0.5 g/kg) in combination with cyclosporin A (30 mg/kg by gavage every other day for 3 months), microscopic examination revealed that Cordyceps could reduce chronic interstitial edema-hemorrhage-fibrosis and tubular denaturation-necrosis in the rat kidney, when compared to control rats that received only cyclosporin A (Zhao and Li, 1993a). These morphological benefits were associated with lower BUN in the Cs-4 group after 8 (−19.4%) and 10 weeks (−39.3%) treatment and reduced secretion of endogenous EGF in urine (all $p < 0.01$), compared to that observed in cyclosporin A controls.

A histological study of renal damage was performed in rats after a combined therapy with: (1) natural Cordyceps and cyclosporin A in an acute experiment, or (2) natural Cordyceps and cyclosporin A in a subchronic study (Zhao and Li, 1993b). Observations were compared with those in control rats treated with only cyclosporin A. In both the acute and subchronic studies, natural Cordyceps prevented morphological damages induced by cyclosporin A (Table 7).

After the results in animals, protective effects of natural Cordyceps against kidney damage by aminoglycoside antibiotics were examined in senior patients with no history of renal diseases (Bao et al., 1991). The patients were given amikacin (intramuscular injection or intravenous perfusion) for treatment of their acute

TABLE 7. RENAL-PROTECTIVE FUNCTIONS OF NATURAL CORDYCEPS ON MORPHOLOGY OF RAT KIDNEYS WITH RENAL DAMAGE INDUCED BY CYCLOSPORIN A

		Cyclosporin A + placebo	*Cyclosporin A + Cordyceps*	p *value*
Experiment 1	*n*	12	12	
Area of proximal convoluted tubule		1.00 ± 0.19	1.27 ± 0.20	<0.01
Area of distal convoluted tubule		1.00 ± 0.20	1.87 ± 0.44	<0.01
Experiment 2	*n*	26	26	
At 2 weeks				
Area of proximal convoluted tubule		1.00 ± 0.14	1.05 ± 0.13	<0.05
Area of distal convoluted tubule		1.00 ± 0.25	1.09 ± 0.22	<0.05
Area of glomerulus		1.00 ± 0.13	1.27 ± 0.20	<0.05
Area of interstitium		1.00 ± 0.16	0.94 ± 0.14	>0.05
At 4 weeks				
Area of proximal convoluted tubule		1.00 ± 0.12	1.38 ± 0.26	<0.05
Area of distal convoluted tubule		1.00 ± 0.21	1.39 ± 0.55	<0.05
Area of glomerulus		1.00 ± 0.15	1.15 ± 0.20	<0.01
Area of interstitium		1.00 ± 0.13	0.68 ± 0.24	<0.05

Rats were treated with cyclosporin A (experiment 1: 50 mg/kg for 15 days; experiment 2: 30 mg/kg for 3 months), in combination with either placebo or natural Cordyceps (experiment 1: 1.0 g/kg; experiment 2: 0.5 g/kg).

Data are adapted from Zhao and Li (1993) and are expressed as fractions of mean values for placebo controls.

infectious diseases: acute recurrence of chronic bronchitis, pneumonia, pleuritis, acute upper respiratory infection, and acute enteritis. With double the dose on the first day, patients in the experimental group received natural Cordyceps in combination with the amikacin treatment. Patients in a control group received the amikacin treatment plus placebo capsules. After the therapy, accumulated 24-hour urinary NAG was found to have significantly increased 4 times from the pretreatment baseline after the therapy in the control group, while it had only doubled from the baseline in the Cordyceps-treated group, which was significantly lower than controls (Table 8).

Cs-4 has been also used to treat patients with gentamicin toxicity. In an open-label, controlled clinical trial (Bi et al., 1994), patients diagnosed with gentamicin nephrotoxic damage were given Cs-4 daily, while another 28 patients with gentamicin toxicity in a control group received cotreatment with gentamicin, adenosine triphosphate (ATP), coenzyme-A, and cytochrome-C. The rate of 6-day complete clinical recovery was significantly higher in the experimental group than in the control group ($p < 0.01$), and the number of days required for urine tests to become normal was significantly lower in the Cs-4 group compared to controls (Table 9).

Postsurgical care has greatly benefited from the ability of cyclosporin A to reduce immune rejection by organ recipients. However, nephrotoxicity of cyclosporin A (a potent immune suppressor) has been a clinical problem during solid organ transplantation, especially kidney transplantation. A clinical study showed that the combined use of a fermented mycelial product of Cordyceps (East-China Pharmaceuticals, Hangzhou, China) and cyclosporin A (5 mg/kg per day) for 15 days in 30 kidney transplant patients produced better clinical outcomes than in controls receiving

TABLE 8. CHANGES OF URINARY N-ACETYL-β-D-GLUCOSAMINIDASE (NAG) IN PATIENTS RECEIVING AMIKACIN TREATMENT AND RENAL PROTECTIVE ACTIVITY OF NATURAL CORDYCEPS

	NAG		
	Placebo group	*Cordyceps group*	p *value*
n	9	10	
Pretreatment	1.00 ± 0.44	0.94 ± 0.36	
At the first day	1.51 ± 0.86	1.03 ± 0.44	
At the third day	2.41 ± 1.45	1.42 ± 0.61	
At the sixth day	3.84 ± 2.28	1.98 ± 0.92	<0.05

Senior patients (53–73 years old) were treated with amikacin (0.4 g/day for 6 days), with either placebo or natural Cordyceps (6 g/day) for 7 days.

Data are adapted from Bao et al. (1991) and are expressed as fractions of mean pretreatment values for the placebo group.

TABLE 9. CLINICAL IMPROVEMENT IN PATIENTS WITH GENTAMICIN NEPHROTOXICITY AFTER Cs-4 TREATMENT

	Control	*Cs-4*	p *value*
n	28	29	
Recovery rate at the sixth day	45%	89%	<0.01
Urine test recovery (days)	6.9 ± 2.1	3.8 ± 1.1	<0.01

Patients with gentamicin nephrotoxic damage were treated with either conventional therapy (adenosine triphosphate [ATP], co-enzyme A, and cytochrome-C), or Cs-4 (4.5 g/day) for 6 days.

Data are adapted from Bi et al. (1994).

only cyclosporin A (Xu et al., 1995). Mild increases in SCr, BUN, and NAG were found in those patients receiving the combined treatment, compared to significant increases in a control group that received only cyclosporine A (Table 10).

Therefore, both clinical and animal studies have demonstrated renal-protective effects of Cordyceps against nephrotoxicity of aminoglycosides and cyclosporin A.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

The meanings of some medical terms in TCM are based on their own definition and philosophy, which are sometimes distinct from those in Western medicine. For example, the meaning of "lung" disease in TCM is much broader than that assigned to it in modern medicine; eg, shortness of breath due to limited heart functions may still be under the "lung" disease category. Therefore, although Cordyceps is mainly used to treat respiratory and renal diseases under these TCM categories, it has been used extensively in treating cardiovascular diseases. For instance, the treatment of arrhythmias with Cordyceps and its mycelial fermentation products is reported to have a rate of efficacy ranging from 75% to 88% (Table 11) (Tang and Jiang, 1994; Li et al., 1985; Liu et al., 1990; Xu and Zheng, 1994; Yan et al., 1992a).

In a 3-month, open-label clinical trial, Cs-4 was used to treat 38 elderly patients with varying degrees of intractable arrhythmias caused by varying forms of heart disease (Tang and Jiang, 1994). Among them, the majority diagnosed with superventricular arrhythmia experienced complete or partial recovery of their ECG with clinical improvement (Table 12). Among patients suffering from ventricular arrhythmia or complete blockage of the right branch, the majority gained complete or partial recovery of their ECG. The investigators concluded that Cs-4 appears not only to be effective for tachyarrhythmia, but also for bradyarrhythmia, and that the longer the therapy, the better the clinical improvement.

A randomized, double-blind, placebo-controlled trial (Xu and Zheng, 1994) demonstrated that treatment using another cultured mycelial Cordyceps product, known as Ningxinbao capsule (*Cephalosporium sinensis*), appeared very effective in completely or partially improving ECG in patients with atrial or ventricular premature beats, as compared to placebo controls. The total effective rate for the treatment group was significantly higher compared to the control group (Table 13).

In an 8-week controlled clinical trial, Cs-4 (3 g/day, for 8 weeks) was used to treat 20 patients with ischemic heart disease, as compared to Persantine (dipyridamole, 150 mg/day, Boehringer Ingelheim, Germany) (Che and Lin, 1996). In addition to the significant reduction

TABLE 10. CLINICAL IMPROVEMENT FROM NATURAL CORDYCEPS IN PATIENTS WITH CYCLOSPORIN A NEPHROTOXICITY

		Urinary NAG		*Serum creatinine*		*BUN*	
	n	*Pre*	*15th day*	*Pre*	*15th day*	*Pre*	*15th day*
Control	39	1.00 ± 0.42	1.42 ± 0.42	1.00 ± 0.13	1.26 ± 0.21	1.00 ± 0.18	1.82 ± 0.18
Cordyceps	30	1.00 ± 0.33	1.17 ± 0.42	1.04 ± 0.08	1.08 ± 0.06	0.91 ± 0.18	1.36 ± 0.27
p value			<0.05		<0.05		<0.05

Patients who received kidney transplantation surgery were treated with cyclosporin A (5 mg/kg per day) in combination with either placebo or fermented mycelia of Cordyceps (3 g/day) for 15 days.

Data are adapted from Xu et al. (1995).

TABLE 11. SUMMARY OF CLINICAL EFFICACY OF CORDYCEPS IN THE TREATMENT OF ARRHYTHMIAS

Reference		*Dose (g/kg)*	*Treatment (week)*	n	*Improved* n	*Improved* %
Tang and Jiang (1994)	Cs-4	3	1	38	31	81.6%
Lie et al. (1985)	*Cephalosporium sinensis*	1.5	2	200	149	74.5%
Liu et al. (1990)	*Cephalosporium sinensis*	3	4	37	30	81.1%
Xu and Zheng (1994)	*Cephalosporium sinensis*	3	2	32	25	78.1%
Yan et al. (1992a)	*Cephalosporium sinensis*	1.5	12	50	44	88.0%

Patients with arrhythmia were treated with different mycelial fermentation products of Cordyceps (dose and length of treatment indicated).

Data are adapted from references: Tang and Jiang (1994); Li et al. (1985); Liu et al. (1990); Xu and Zheng (1994); Yan et al. (1992a).

of total cholesterol, triglycerides, and β-lipoprotein as shown in Part I, Table 15 (Zhu et al., 1998), 87%–90% of patients experienced clinical improvement of their chest distress and palpitation. The majority of the patients (65%) had improved ECG after treatment, which was similar (if not better) compared to 55% in the control group. Moreover, blood fibrinogen and viscosity was significantly reduced (Table 14).

TABLE 12. ECG IMPROVEMENT OF ARRHYTHMIAS BY Cs-4 TREATMENT

	n	*Improved* n	*Improved* %
Superventricular arrhythmia	24	20	83%
Ventricular arrhythmia	10	8	80%
Complete blockage of the right branch	4	3	75%
Total	38	31	81.6%

Patients with arrhythmia of varying types were treated with Cs-4 (3 g/day) for 3 months.

Data are adapted from Tang and Jiang (1994).

TABLE 13. CLINICAL IMPROVEMENT OF PREMATURE BEATS AFTER 2-WEEK NINGXINBAO (*CEPHALOSPORIUM SINENSIS*) TREATMENT

	Atrial premature beats			*Ventricular premature beats*		
		Improved			*Improved*	
	n	n	%	n	n	%
Placebo	18	4	22.2%	10	1	10.0%
Ningxinbao	17	14	82.4%	13	11	84.6%
p value		<0.01			<0.01	

In a randomized, double-blind, placebo-controlled trial, patients with arrhythmia were treated with Ningxinbao capsule at a dose of 1.5 g/day for 2 weeks.

Data are adapted from Xu and Zheng (1994).

The benefits of long-term use of Cs-4 were evaluated in a group of 64 patients with chronic heart failure (Chen, 1995). Patients in one group were treated with Cs-4 in addition to their maintenance therapy for heart failure, and compared to control patients who received only the basic therapy for their heart failure. According to the New York Heart Association (NYHA) functional classification system for cardiac functions, the Cs-4 treatment seemed not to have significantly improved their mortality as compared to controls ($p > 0.05$). However, echocardiography demonstrated a significant reduction in the heart rate and a significant increase in the cardiac stroke volume and cardiac index (= cardiac output ÷ body surface area) as compared to controls (Table 15). Using the Yale evaluation system to analyze quality of life, the shortness of breath-fatigue index was significantly increased in these patients after the Cs-4 adjuvant therapy, in contrast to the control group under the basic maintenance treatment. As analyzed earlier, the Cs-4 adjuvant therapy dramatically improved general physical and emotional conditions of the patients with chronic heart failure (see Part I, Table 5 for details, Zhu et al., 1998). This study suggests that long-term Cs-4 treatment may dramatically improve the quality of life of chronic heart failure patients, together with improvement of their cardiac functions.

Animal studies, *in vivo* or with isolated organs, have attempted to explore the underlying mechanism of the cardiovascular benefits of Cordyceps. Pharmacological activities of natural Cordyceps and its mycelial fermenta-

TABLE 14. CLINICAL IMPROVEMENT AND CHANGES OF BLOOD FIBRINOGEN AND VISCOSITY IN ISCHEMIC HEART DISEASE PATIENTS IN RESPONSE TO CS-4 TREATMENT

		Pretreatment	*Post-treatment*	p *value*
Fibrinogen (g/L)		4.10 ± 0.67	3.80 ± 0.56	<0.01
Plasma viscosity (CP)		1.87 ± 0.10	1.76 ± 0.08	<0.01
Whole blood viscosity	high shear (CP)	10.3 ± 3.20	6.28 ± 2.40	<0.001
	low shear (CP)	9.60 ± 1.80	7.60 ± 2.40	<0.01

Patients (n = 40) with ischemic heart disease were treated with Cs-4 (3 g/day, for 8 weeks).

Data are adapted from Che and Lin (1996).

tion products on the cardiovascular system examined on preclinical animal and isolated tissues are summarized below and in Table 16.

(1) Dilation of arteries and improvement of nutritional blood supply to organs and extremities

Dilation of arteries in animals or of isolated arteries by natural Cordyceps or its fermentation products has been documented, including dilation of aorta, coronary arteries, cerebrovasculature, and peripheral arteries.

a) Relaxation of contracted aorta. Artery relaxation was seen in an isolated aorta preparation after water extracts of a mycelial fermentation product (SMIH8819) added to a perfusion solution at a concentration of 50 μg/mL, when aorta was in a persistently contracted condition pre-evoked by addition of 50 mM K^+ (Tsunoo et al., 1995).

b) Hypotensive effects in extremities. After intravenous injection of Cs-4 (60 mg/kg), anesthetized dogs displayed a significant decrease in blood pressure ($p < 0.001$ at peak; $p < 0.02$ at 1 to 15 minutes) (Feng et al., 1987). Lower doses of Cs-4 treatment (2.5, 5, or 10 mg/kg, intravenously) did not display such systematic hypotensive effects, but induced a dramatic decrease in femoral arterial resistance (all $p <$ 0.02). When the sciatic nerve and the femoral nerve were severed unilaterally, the hypotensive effects of Cs-4 in the femoral artery on the affected side appeared to be moderately muted (from a 45% decrease to a 20% decrease). This indicated that the hypotensive effects were partially mediated by functions of motor nerves. Although there were dramatic changes in resistance and pressure of femoral artery after the Cs-4 treatment, whole body blood pressure of the dogs remained unchanged when Cs-4 was

TABLE 15. IMPROVEMENT OF SHORTNESS OF BREATH/FATIGUE INDEX AND HEART FUNCTIONS OF PATIENTS WITH CHRONIC HEART FAILURE IN RESPONSE TO LONG-TERM CS-4 ADJUVANT TREATMENT

	Control	*Cs-4*	p *value*
n	30	34	
Shortness of breath/fatigue index			
Index score after treatment	1.00 ± 0.08	1.27 ± 0.13	<0.01
Increase after treatment	1.00 ± 0.48	2.48 ± 0.61	<0.01
Average percentage increase	25%	66%	
Heart rate (beat/min)	1.00 ± 0.06	0.90 ± 0.05	<0.01
Stroke volume (mL)	1.00 ± 0.23	1.21 ± 0.13	<0.01
Cardiac index (cardiac output ÷ body surface area)	1.00 ± 0.22	1.19 ± 0.22	<0.01

Patients with chronic heart failure were treated with either Cs-4 or placebo (3–4 g/day, for 26 ± 3 months) in addition to standard treatments for chronic congestive heart failure.

The shortness of breath/fatigue index was assessed according to the Yale grading system. Heart rate and other cardiac function parameters were measured by echocardiography.

Data are adapted from Chen (1995) and are expressed as fractions of mean values of those observed for controls who received only standard treatments.

TABLE 16. SUMMARY OF PRECLINICAL EXAMINATIONS OF CARDIOVASCULAR EFFECTS OF CORDYCEPS

		Treatment	*Results*	*Reference*
Isolated Aorta	SMIH8819	50 μg/mL in medium	Relax aorta	Tsunoo et al. (1995)
Dogs	Cs-4	60 mg/kg, i.v.	Lower blood pressure	Feng et al. (1987)
Dogs	Cs-4	2.5–10 mg/kg, i.v.	Lower femoral arterial resistance	Feng et al. (1987)
Dogs	Cs-4	2.5–10 mg/kg, i.v.	Lower cerebro-arterial resistance	Feng et al. (1987)
Dogs	Cs-4	0.425 g/kg, i.v.	Increase coronary blood flow	Feng et al. (1987)
Dogs	Cs-4	0.425 g/kg, i.v.	Lower coronary arterial resistance	Feng et al. (1987)
Dogs	Cs-4	0.425 g/kg, i.v.	Lower heart rate	Feng et al. (1987); Lou et al. Cardiovascular pharmacological studies of Cordyceps fementation solution. Unpublished report, Beijing Medical University and Lanzhou National College, 65–68; Lou et al. (1986)
Dogs	Cs-4	0.25–0.5 g/kg, i.v.	Against arrhythmia induced by aconitine or barium chloride	Lou et al. (1986)
Guinea pigs	Natural Cordyceps	1.0 g/kg, i.p.	Against arrhythmia induced by Quabain	Mei et al. (1989)
Rabbits	Cs-4	150 mg/kg, i.v.	Against myocardial ischemia induced by Pituitrin	Lou et al. (1986)
Rats	Cs-4	0.9 g/kg, i.g.	Against stress-induced myocardial infraction	Lou et al. (1986)
Platelets	Cs-4	2–4 mg/mL in medium	Against platelet aggregation Against thrombosis	Lou et al. (1986)
Rabbits	CsB-851	30 μg/kg/min, i.v.	Against thrombosis	Zhao et al. (1991)

Animals, isolated organs, and cells were treated with natural Cordyceps or its fermentation products as indicated.
Data are adapted from references: Tsunoo et al. (1995); Feng et al. (1987); Lou, Lu, Liao. Cardiovascular pharmacological studies of Cordyceps fermentation solution. Unpublished report, Beijing Medical University and Lanzhou National College, 65–68; Lou et al. (1986); Mei et al. (1989); Zhao et al. (1991).

administered through the femoral artery (Feng et al., 1987; Feng, Zhou, Feng, Shuai. Pharmacological studies on fermented mycelia of Cordyceps. Unpublished report, Jianxi Medical College, pp. 45–52.)

The investigators attempted to explore the mechanisms of the arterial dilation produced. Administration of Cs-4 (60 mg/kg) to dogs through the vertebral artery induced a dramatic 48% reduction in blood pressure, while the same dose of Cs-4 could not induce a reduction of blood pressure in the animals (Feng, Zhou, Feng, Shuai. Pharmacological studies on fermented mycelia of Cordyceps. Unpublished report, Jianxi Medical College, 45-52.) The authors believed that such systematic hypotensive effects might be at least partially due to an effect on the central nervous system. Further experiments demonstrated that the effect of Cs-4 on the vasculature was not mediated by stimulation or inhibition of either α- or β-adrenogenic or histamine receptors, but may be via direct dilatory effects of Cs-4 or partially mediated by M cholinergic receptors (Feng et al., 1987).

c) Dilation of coronary arteries and increased blood supply to the heart. Cs-4 can dilate the coronary arteries, in addition to dilation of the cerebrovasculature and peripheral arteries (Feng et al., 1987). When dogs were administered extracts of Cs-4 (0.425 g/kg, intravenously) under anesthesia, the resistance of coronary arteries was significantly decreased by 49% ($p < 0.01$), with a dramatic reduction of coronary blood pressure (−116.5% on average, $p < 0.01$) and heart rate (−14% on average, $p < 0.05$). Subsequently, the volume of coronary arterial blood flow was dramatically increased (+100% at peak and +35% at 1 minute, both

$p < 0.01$). Injection of normal saline in a control group showed no significant change in resistance and blood volume of the coronary system.

d) Dilation of cerebrovascular arteries and increased blood supply to the brain. After anesthetized dogs ($n = 7$) were treated with Cs-4 (0.6 g/kg, intravenously), vertebral arterial resistance decreased by an average of 75% ($p < 0.05$), (Feng et al., 1987), which indicated that Cs-4 can also dilate the cerebrovasculature. In separate experiments, reductions in vertebral arterial resistance were reported as a function of Cs-4 (5 and 10 mg/kg) when given through the vertebral artery ($-25\%, p < 0.05$; and -32%, $p < 0.01$) (Feng et al., 1987). In these experiments, the reductions in arterial resistance following low dosages of Cs-4 were not associated with significant changes in blood pressure of the whole body, indicating reposition of blood circulation. In control groups with injections of equal volumes of normal saline, only a small reduction (1% to 3%) of arterial resistance was seen.

(2) Reducing the heart rate

Natural Cordyceps and its mycelial fermentation products, such as Cs-4 (either an ethanol extract or a concentrate of the fermentation solution), were also effective in reducing the heart rate (Feng et al., 1987; Lou et al., 1986). The negative chronotropic action was also demonstrated in an isolated right cardiac atrium experiment ($p < 0.05$) with no apparent effect on myocardiac contractility (Lou, Lu, Liao. Cardiovascular pharmacological studies of Cordyceps fermentation solution. Unpublished report, Beijing Medical University and Lanzhou National College, pp. 65–68).

(3) Antiarrhythmic effects

Cs-4 ethanol extract was studied for its antiarrhythmic effects in animals with experimental arrhythmias (Lou et al., 1986). Cs-4 (0.5 g/kg, i.v.) prolonged the induction period of arrhythmia ($n = 10, p < 0.01$) onset induced by administration of aconitine (0.25–0.33 g/kg, i.v.) and shortened the duration of the arrhythmias ($p < 0.001$) when compared with control rats treated only with placebo ($n = 11$). The majority of arrhythmias occurring in the Cs-4-treated rats were atrial arrhythmias and bigeminal or trigeminal arrhythmias. These were generally much less severe, as a rule, in contrast to those occurring in the control group (ie, ventricular arrhythmias as the majority of arrhythmias, receiving only placebo).

Cs-4 (0.25 g/kg, i.v., $n = 7$) was also effective in shortening the duration of the arrhythmias induced by barium chloride (1 mg/kg, i.v.) ($p < 0.02$) when compared to the control group ($n = 7$), although it was not effective in prolonging the induction period of arrhythmia onset (Lou et al., 1986). The authors also observed that during the experimental arrhythmias, intermittent normal sinus rhythm occurred in the Cs-4 treated group.

Similar antiarrhythmic effects were also found after administration of natural Cordyceps (0.5 or 1.0 g/kg, i.p.) when aconitine (1.2 mg/kg, i.p.) was used to induce experimental arrhythmias (Mei et al., 1989). In addition, the authors demonstrated that natural Cordyceps (1.0 g/kg, i.p.) could significantly enlarge arrhythmia-inducing doses of ouabain (+30% on

TABLE 17. THERAPEUTIC EFFECTS OF A 3-MONTH TREATMENT WITH A CULTIVATED MYCELIAL PRODUCT OF CORDYCEPS IN 33 PATIENTS WITH CHRONIC ACTIVE HEPATITIS B

TTT was recovered or improved	in 71.9% patients	
GPT was recovered or improved	in 78.6% patients	
Positive-to-negative conversion of HbsAg occurred	in 35.5% patients	
Albumin was increased	10.8 ± 2.54%	$p < 0.001$
γ-Globulin was decreased	10.3 ± 1.79%	$p < 0.001$

Thirty-three patients with chronic active hepatitis B were treated with a cultivated mycelial product of Cordyceps (*Mortierella hepiali* Chen lu *Sp. nov.*) (3.75 g/day) for 3 months.
TTT, thymol turbidity test.
Data are adapted from Zhou et al. (1990).

average, $p < 0.05$ to <0.01). It was found that the antiarrhythmic effects of natural Cordyceps were not due to prolonging functional refractory period, nor altering automatic rhythmicity.

(4) Effects against acute myocardial ischemia and stress-induced myocardial infarction

Natural Cordyceps and its mycelial fermentation products are active in protecting against experimental myocardial ischemia and acute myocardial infarction (Lou, Lu, Liao. Cardiovascular pharmacological studies of Cordyceps fermentation solution. Unpublished report, Beijing Medical University and Lanzhou National College, pp. 65–68; Lou et al., 1986) As described earlier, a fermented mycelial product of Cs-4 could reduce oxygen consumption in animals under experimental conditions and had dramatic anti-anoxic effects in general (Part I, Table 4) (Zhu et al., 1998). In rabbits (Lou, Lu, Liao. Cardiovascular pharmacological studies of Cordyceps fermentation solution. Unpublished report, Beijing Medical University and Lanzhou National College, pp. 65–68), a fermented mycelial preparation of Cs-4 (0.15 g/kg, i.v.) was particularly effective ($p < 0.05$) against acute myocardial ischemic ECG changes induced by pituitrin (1.5 U/kg, i.v.). Injection of the Cs-4 preparation (0.9 g/kg, i.g.) from a fermentation solution significantly prevented orthostatic elevation of T wave and elevation of S-T segment ($p < 0.01$) in rats treated with thyroxin (60 mg/rat, i.g.) and noradrenaline (100 mg/rat, i.p.), indicating preventive effects against myocardial ischemia (Lou et al., 1986).

When rats were administrated Cs-4 and thyroxin for 7 consecutive days and noradrenaline on the eighth day, changes in Q wave, S-T segment, and T wave during ECG examination were less severe compared to those in the saline control group (Lou et al., 1986). This suggested that Cs-4 might protect rats from severe damage due to stress-induced myocardial infarction. However, on pathological examination without instrumentation, the authors did not find significant differences between the experimental and the control groups.

(5) Effects of thrombosis and anti-aggregation of platelets

In studies with normal platelet-rich plasma, both Cs-4 and Cs-4 fermentation solution preparations (5 or 10 mg/2.5 mL) were effective against platelet aggregation induced by addition of either collagen or adenosine diphosphate (ADP). When compared with the controls, the aggregation rate of platelets after treatment with Cs-4 appeared to be significantly lower ($p < 0.005$ or < 0.001). A lower dose of Cs-4 (1 or 2.5 mg/2.5 mL) had no significant anti-aggregation activity (Lou et al., 1986).

In studies with rabbits, a preparation of concentrated Cs-4 (CsB-851, 30 or 90 μg/kg per minute, i.v.) significantly inhibited the aggregation of ^{51}Cr-labeled platelets in the de-endothelial abdominal aorta: by -51% and -71% ($p < 0.01$), respectively (Zhao et al., 1991).

EFFECTS ON THE HEPATIC SYSTEM

Mycelial fermentation products of Cordyceps (XinGanBao and another cultured mycelial product) have been used clinically for the treatment of chronic hepatitis and related disease conditions.

In an open-label clinical study, 33 patients with chronic active hepatitis B (8 diagnosed with cirrhosis) were treated with a cultivated mycelial product of Cordyceps (*Mortierella hepiali* Chen lu sp. nov.) (Zhou et al., 1990). The investigators reported that after the treatment, the thymol turbidity test (TTT) returned to normal in almost a third of the patients who showed an abnormal TTT result prior to the therapy (Table 17). Among the patients with increased serum glutamic-pyruvic transaminase (SGPT), well over half recovered to a normal range. In addition, there was an average 20% increase in serum albumin and an average 29% decrease in γ-globulin after the 3-month treatment.

A cultured mycelial fermentation product of Cordyceps (Nantong Biochemical Pharmaceuticals) was used to treat 22 patients with post-hepatitis cirrhosis (Liu et al., 1986). Associated with a dramatic improvement in symptoms, a

TABLE 18. THERAPEUTIC EFFECTS OF A 3-MONTH TREATMENT WITH A CULTIVATED MYCELIAL PRODUCT OF CORDYCEPS IN 22 PATIENTS WITH POST-HEPATITIS CIRRHOSIS

Ascites	Disappearance in 70.6% patients, improved in 29.4% patients		
Albumin	Increased	0.46 ± 0.12 g/dL	$p < 0.001$
	Increased >0.5 g/dL	in 11 (50%) patients	

Protein electrophoresis	*Pretreatment*	*Post-treatment*	p *value*
Albumin	49.0% ± 6.46%	52.5% ± 6.58%	<0.01
γ-Globulin	36.1% ± 7.58%	32.6% ± 6.86%	<0.05

Twenty-two patients with post-hepatitis cirrhosis were treated with a cultivated mycelial product of Cordyceps (Nantong Biochemical Pharmaceuticals) (6–9 g/day) for 3 months.

Data are adapted from Liu et al. (1986).

significant increase in serum albumin was observed from the baseline and there was also a decrease in γ-globulin after the treatment (Table 18). In this group of cirrhotic patients, the treatment did not appear to significantly change SGPT and TTT.

In another open-labeled, controlled clinical trial, XinGanBao was used to treat 70 patients with chronic hepatitis B and post-hepatitis cirrhosis (Yang et al., 1994). A significant clinical response was reported for 68% of patients in the XinGanBao treatment group. This total effective rate was comparable to the 57% of patients who responded in a positive control group who showed clinical improvement after treatment with a known effective herbal medicine (ShuShe combo tablet, containing *Ganoderma applanatum* [Pers.] Pat. as the main ingredient). Increases in A/G ratio and decreases in TTT and SGTP were similar in the experimental and positive control groups (Table 19).

XinGanBao capsule was also studied in the treatment of 83 asymptomatic hepatitis B virus carriers in an open-labeled clinical trial (Xie, 1992). The authors reported a high total effective rate and that in a good many patients there was a positive-to-negative conversion of detectable hepatitis B surface antigen, while a lower titer of the surface antigen occurred in just under half of the patients (Table 20).

In an open-label study, Cs-4 was used to treat 53 patients diagnosed with liver cirrhosis complicated with upper gastrointestinal bleeding at the terminal stage of schistosomiasis (Yang, 1995). After treatment for 2 or 3 months, subjective symptoms were dramatically improved in all patients. B-ultrasound examination revealed a dramatic reduction in the diameter of the portal vein in over two-thirds of the patients with a pretreatment diameter greater than 13 mm (Table 21). It should also be noted that among those patients who did not show a significant reduction in the diameter of the portal vein, a reduction in the diameter of the portal vein branches and/or spleen vein was found. Esophagogastric endoscopy revealed apparent improvements to a different extent in esophageal/cardiac varices.

TABLE 19. THERAPEUTIC EFFECTS OF A 3-MONTH TREATMENT WITH XINGANBAO IN PATIENTS WITH CHRONIC HEPATITIS B OR POST-HEPATITIS CIRRHOSIS

		Changes after treatment		
	n	*A/G ratio*	*TTT*	*GPT*
Positive control	35	+0.29 ± 0.39	−2.09 ± 3.45	−52.4 ± 88.3
XinGanBao	35	+0.35 ± 0.88	−1.33 ± 3.05	−75.5 ± 60.3
p value		>0.05	>0.05	>0.05

Seventy patients with chronic hepatitis B or post-hepatitis cirrhosis were treated with XinGanBao (4.5 g/day) or, as a positive control, *G. applanatum* combo tablet (4.5 g/day) for an average of 71 days.

A/G ratio, Albumin/Globulin ratio; TTT, thymol turbidity test; GPT, glutamic-pyruvic transaminase.

Data are adapted from Yang et al. (1994).

TABLE 20. CHANGES IN HEPATITIS B SURFACE ANTIGEN (HBSAG) TITER AFTER A 3-MONTH TREATMENT WITH XINGANBAO CAPSULE IN 83 ASYMPTOMATIC HEPATITIS B VIRUS CARRIERS

	HbsAg titer		
n	⟶ *Negative*	*Decreased*	*No change*
83	33 (39.8%)	39 (47.0%)	11 (13.3%)

Eighty-three asymptomatic hepatitis B virus surface antigen carriers were treated for 3 months with XinGanBao capsule: 2–4 years old, 0.25 g/day; 4–6 years old, 0.5 g/day; 10–15 years old, 1.25 g/day; >16 years old, 1.5 g/day.

Data are adapted from Xie (1992).

EFFECTS ON BLOOD GLUCOSE METABOLISM

Tested for hypoglycemic effects in animals, ethanol-alkaline extracts of XinGanBao were administrated to normal mice (500 mg/kg, i.g.) and produced a significant decrease in blood glucose at 3 and 6 hours after the treatment, as compared to placebo controls (both $p < 0.05$) (Ji et al., 1993). The hypoglycemic effect persisted for 24 hours after the treatment ($p < 0.05$). The authors also observed a more dramatic decrease in blood glucose with intraperitoneal administration of the extracts (100 mg/kg) in normal mice. In other experiments, using diabetic animal models created by treatment of mice with either alloxan or sterptozotocin (STZ), blood glucose was significantly reduced by the extract, as compared to the placebo control group ($p < 0.05$ to < 0.01). The authors suspected that the hypoglycemic effects were mediated by component polysaccharides that were identified by paper chromatography. The polysaccharides consist of five major monosaccharides: L-arabinose, L-xylose, D-mannose, D-galactose, and D-glucose.

In other animal studies, CS-F30, a purified polysaccharide (molecular weight [MW] 45,000) isolated from a fermented mycelial Cordyceps product, exhibited potent hypoglycemic activity after oral administration in mice (first panel, Table 22) (Kiho et al., 1993). By injection (intraperitoneal or intravenous), CS-F30 caused more dramatic hypoglycemic effects: plasma glucose was reduced in normal and diabetic mice (other panels, Table 22) (Kiho et al., 1996). Yet it was not associated with significant alterations of plasma insulin. It was further demonstrated that CS-F30 could markedly increase the activity of hepatic glucokinase, hexokinase, and glucose-6-phosphate dehydrogenase (Table 23).

In the clinic, Cs-4 was studied in a randomized trial in diabetic patients (Guo and Zhang, 1995). Patients in the treatment group who received Cs-4 in conjunction with other traditional Chinese herbs achieved a significantly greater total effective rate than a control group of patients who received the other herbal medicines without Cs-4 (Table 24). In addition, a positive urinary protein test became negative in half the patients in the treatment group, as compared to none in the control group.

TABLE 21. REDUCTION OF THE PORTAL VEIN DIAMETER AFTER A 2- OR 3-MONTH TREATMENT WITH CS-4 IN 39 PATIENTS WITH CIRRHOSIS

	Reduction in the diameter	
	n	*Average reduction*
After 2 or 3 months	26 (68.4%)	3.53 or 3.43 mm (ranging from 1–9 mm)

Fifty-three patients with terminal stage of schistosomiasis and cirrhosis complicated with upper GI bleeding were treated for 2 or 3 months with Cs-4 (7.2 g/day). Among them, 39 had a portal vein diameter of >13 mm.

Data are adapted from Yang (1995).

EFFECTS ON THE IMMUNE SYSTEM AND TREATMENT OF DISEASES OF THE IMMUNE SYSTEM

Various effects of Cordyceps on the immune system have been reported; however, the experimental results have been controversial with both potentiating and inhibiting effects. While the observed effects were probably due to different experimental conditions, one may assume that Cordyceps is a bi-directional modulator of the immune system.

It was reported that Cordyceps could enhance phagocytosis of macrophages (Jia and Lau, 1997; Zhang et al., 1985) in addition to numerous reports that Cordyceps could induce increases in spleen weight (including increas-

TABLE 22. DECREASE IN BLOOD GLUCOSE IN MICE AFTER TREATMENT WITH CS-F30 (AN ISOLATED POLYSACCHARIDE FROM A MYCELIAL STRAIN OF CORDYCEPS)

		n	Dose (mg/kg)		Blood glucose			
					Pretreatment	*At 3 hours*	*At 6 hours*	*At 24 hours*
Normal mice	Control	5			1.00	0.93 ± 0.02	0.94 ± 0.01	0.83 ± 0.03
	CS-F30	5	50, p.o.		1.00	0.84 ± 0.05	0.76 ± 0.07	0.83 ± 0.05
				p value:		>0.05	<0.05	>0.05
Generic diabetic mice	Control	5			1.00	0.81 ± 0.05	0.90 ± 0.04	0.99 ± 0.01
	CS-F30	5	50, i.p.		1.00	0.42 ± 0.03	0.28 ± 0.02	0.49 ± 0.09
				p value:		<0.001	<0.001	<0.001
Normal mice	Control	5			1.00	0.88 ± 0.06	0.93 ± 0.02	0.93 ± 0.01
	CS-F30	5	10, i.v.		1.00	0.68 ± 0.03	0.65 ± 0.04	0.80 ± 0.01
				p value:		<0.05	<0.001	<0.01
STZ diabetic mice	Control	5			1.00	0.97 ± 0.02	0.97 ± 0.04	1.00 ± 0.04
	CS-F30	5	10, i.v.		1.00	0.53 ± 0.07	0.52 ± 0.01	1.00 ± 0.04
				p value:		<0.001	<0.001	>0.05

Both normal and diabetic mice were treated with CsB-F30 at the doses indicated. Blood was collected prior to and at 3, 6, and 24 hours after treatment for blood glucose analysis. Data are expressed as fractions of mean values of blood glucose observed before treatment in the placebo control group.

p.o., per oral; i.p., intraperitoneal; i.v. intravenous.

Data in the first panel are adapted from Kiho et al. (1993) and data in the other panels from Kiho et al. (1996).

ing spleen DNA biosynthesis) and decreases in thymus weight (Yue et al., 1995; Chen et al., 1985; Liu and Xu, 1985). This enhancement of phagocytosis appeared to be dose-dependent (Table 25). Moreover, the macrophage-stimulatory activity of Cordyceps has been attributed to polysaccharide (Cs-1) components isolated from Cordyceps (Yue et al., 1995). However, when peripheral white blood cells were activated by yeast polysaccharides, Cordyceps inhibited rather than potentiated the activated phagocytosis (Zhu et al., 1990). This inhibitory effect was also produced in a dose-dependent manner (Table 26).

Similar to the effects on phagocytosis described above, the often reported promotion of lymphocyte transformation by Cordyceps has also been controversial and in not a few reports. At minimum, then, under conditions of reduced lymphocyte transformation in chronic

TABLE 23. CHANGES IN LIVER ENZYMES RESPONSIBLE FOR GLUCOSE METABOLISM AFTER TREATMENT WITH CS-F30 IN MICE

	n	Dose (mg/kg)		Enzyme catalytic activity		
				At 3 hours	*At 6 hours*	*At 24 hours*
Glucokinase						
Control	5			1.00 ± 0.11	1.00 ± 0.12	1.00 ± 0.15
CS-F30	5	50, i.p.		2.90 ± 0.17	1.61 ± 0.13	2.50 ± 0.19
			p value:	<0.001	<0.01	<0.001
Hexokinase						
Control	5			1.00 ± 0.05	1.00 ± 0.15	1.00 ± 0.06
CS-F30	5	50, i.p.		1.38 ± 0.15	1.19 ± 0.17	1.32 ± 0.10
			p value:	<0.05	>0.05	<0.05
Glucose-6-phosphate dehydrogenase						
Control	5			1.00 ± 0.13	1.00 ± 0.13	1.00 ± 0.28
CS-F30	5	50, i.p.		2.59 ± 0.39	1.23 ± 0.19	0.99 ± 0.09
			p value:	<0.01	>0.05	>0.05

Normal mice were treated with CsB-F30 at 50 mg/kg, and examined at 3, 6, and 24 hours after treatment.

i.p., intraperitoneal.

Data are adapted from Kiho et al. (1996) and are expressed as fractions of mean values of placebo controls.

TABLE 24. CLINICAL THERAPEUTIC EFFECTS OF Cs-4 IN THE TREATMENT OF DIABETIC PATIENTS

	n	*Improved*	*Not effective*	p *value*
Control	22	12 (54.5%)	10 (45.5%)	0.02
Cs-4	20	19 (95.0%)	1 (5.0%)	
		Positive urinary protein test		
		Pretreatment	*Post-treatment*	
Control	22	6	7	<0.01
Cs-4	20	6	3	

Patients (n = 42) with diabetes were treated either with or without Cs-4 (3 g/day) for 30 days. Those without Cs-4 received other Chinese medicinal herbs (names not given).

Data are adapted from Guo and Zhang (1995).

renal dysfunctional rats, Cordyceps could improve the rate of transformation (Table 27) (Cheng et al., 1992).

Several studies of Cordyceps have focused on natural killer (NK) cells and tumor formation. An *in vitro* study demonstrated that natural Cordyceps was capable of significantly enhancing the activity of NK cells in normal individuals and in leukemia patients (Table 28) (Liu et al., 1992). Further studies revealed that a water extract of natural Cordyceps inhibited NK cell activity in leukemia in the remission stage, but activated NK cell activity in leukemia in the active stage (Table 29) (Cho et al., 1994).

In addition to the augmentation of NK cell activity, natural Cordyceps was shown to prevent decreases of NK cell activity in immune-suppressed mice and to reduce the formation of lung tumor colonies (Table 30) (Xu and Peng, 1988). Similarly, increased NK cell activity was associated with a reduced *in vitro* formation of B16 melanoma (Xu et al., 1992). However, one study reported that two fractions isolated from the fruiting bodies of Cordyceps were capable of inhibiting NK cell activity (Kuo et al., 1996). When K562 cells were incubated with the fractions in a series of concentrations, the activity of the cells was dramatically inhibited with $IC_{50} = 25 \pm 3$ mg/mL for fraction CS-36-39 and $IC_{50} = 13 \pm 6$ mg/mL for fraction CS-48-51.

Chen et al. (1987) reported that an ethanol extract of natural Cordyceps could increase the number of T-helper cells and the ratio of T-helper:T-suppressor cells in mice (Table 31). It was also reported that serum prepared from Cordyceps-treated rats significantly enhanced the *in vitro* production of interleukin-1 (IL-1), interferon (IFN), and tumor necrosis factor (TNF) in Kupffer's cells of the liver (Liu et al., 1996). The increased production was shown to be dose-dependent (Table 32).

Expression of surface molecules of lymphocytes was also influenced by Cordyceps. Expression of interleukin-2 (IL-2) receptor on the surface of peripheral lymphocytes was significantly augmented, as shown in cultured lymphocytes isolated from normal controls and patients with varying kidney diseases treated with natural Cordyceps for 24 hours (Table 33) (Chen and Liu, 1992). In another experiment, rats treated with a polysaccharide (nature not given) preparation isolated from natural Cordyceps showed significantly reduced premature double-positive T cells (CD_4^+/CD_8^+) in thymus, while single-positive CD_4^+ T cells ($CD_4^+/CD8_8^-$) were significantly increased (Table 34) (Shen et al., 1991). In addition, expression of CD surface molecules on spleen lymphocytes was also changed: CD4, CD5, and CD8 increased significantly, and CD25 decreased significantly.

Because of the above profound influence on immune functions, both natural Cordyceps and its mycelial fermentation products have been used in many clinical conditions in patients

TABLE 25. DOSE-DEPENDENT ENHANCEMENT OF PHAGOCYTOSIS OF J774 CELLS BY CS-4 TREATMENT

	Cordyceps concentration (μg/mL)				
	0 (control)	*50*	*100*	*500*	*1000*
Phagocytosis	1.00 ± 0.02	1.18 ± 0.02	1.27 ± 0.04	2.52 ± 0.04	2.51 ± 0.09
p value		>0.05	>0.05	<0.05	<0.05

J774 cells were cultured in the absence or presence of Cs-4 for 1 hour at the incremental concentrations indicated. Phagocytosis was measured by chemoluminescence.

Data are adapted from Jia and Lau (1997).

TABLE 26. CS-4-INDUCED DOSE-DEPENDENT INHIBITION OF PHAGOCYTOSIS OF PERIPHERAL WHITE BLOOD CELLS PREACTIVATED BY YEAST POLYSACCHARIDES

	Concentration of Cs-4 (mg/mL)				
	0	*0.60*	*1.25*	*2.50*	*5.00*
Inhibition of phagocytosis	0	0.21 ± 0.09	0.46 ± 0.15	0.77 ± 0.12	0.99 ± 0.01
p value		<0.05	<0.05	<0.05	<0.05

Peripheral white blood cells pre-activated by yeast polysaccharides were cultured in the absence or presence of Cs-4 at the incremental concentrations indicated.

Data are adapted from Zhu et al. (1990).

TABLE 27. ENHANCEMENT OF LYMPHOCYTE TRANSFORMATION BY NATURAL CORDYCEPS IN CHRONIC RENAL DYSFUNCTIONAL RATS

		Chronic renal dysfunction	
	Normal control	*Control*	*Cordyceps*
Lymphocyte transformation	1.00 ± 0.21	0.29 ± 0.04	0.97 ± 0.22
p value (compared to normal control)		<0.01	>0.05

Rats with chronic renal dysfunction were treated with either placebo or natural Cordyceps (0.5 g/day, i.g.) for 4 months.

Data are adapted from Cheng et al. (1992).

TABLE 28. ACTIVITY ENHANCEMENT BY NATURAL CORDYCEPS OF NATURAL KILLER CELLS ISOLATED FROM NORMAL PATIENTS AND PATIENTS WITH LEUKEMIA

		Activity of NK cells		
	n	*Untreated*	*Cordyceps-treated*	p *value*
Normal controls	5	1.00 ± 0.10	1.74 ± 0.53	<0.05
Leukemia patients	10	0.39 ± 0.24	1.67 ± 0.68	<0.001
p value		<0.01	>0.05	

Natural killer (NK) cells were isolated from peripheral blood of patients with leukemia or normal control subjects and treated with either placebo or natural Cordyceps (12.5 mg/mL) to examine differences in NK cell function.

Data are adapted from Liu et al. (1992) and are expressed as fractions of untreated control cells from normal control subjects.

TABLE 29. NATURAL CORDYCEPS TREATMENT-INDUCED BI-DIRECTIONAL REGULATION ACTIVITY OF *EX VIVO* NATURAL KILLER CELLS DERIVED FROM PATIENTS WITH LEUKEMIA OF DIFFERENT DISEASE STAGES

		Activity of NK cells		
Leukemia stage	n	*Untreated*	*Cordyceps-treated*	p *value*
Remission	10	1.00 ± 0.19	0.45 ± 0.11	<0.01
Active	11	1.00 ± 0.93	2.46 ± 1.25	<0.01

Natural killer (NK) cells were isolated from peripheral blood of patients with leukemia and treated with natural Cordyceps (30 mg/mL) to examine NK cell function.

Data are adapted from Cho et al. (1994) and are expressed as fractions of untreated cells from controls.

with altered immune functions. As noted earlier, their use is found in the treatment of patients with kidney diseases. As a result, Cordyceps-induced suppression of T-cell subgroups has been demonstrated to coincide with improvements in renal function in patients with chronic renal failure (Guan et al., 1992; Chen et al., 1984). An example is shown in Table 35.

TABLE 30. EFFECTS OF NATURAL CORDYCEPS ON NATURAL KILLER CELL ACTIVITY AND LUNG CANCER DEVELOPMENT IN RATS

	n	*Activity of NK cells*	*Weight of lungs*	*Number of tumor colonies*
Control	4	1.00 ± 0.10	1.00 ± 0.13	4 (0–10)
Cordyceps	4	1.25 ± 0.10	0.85 ± 0.15	2 (0–5)
p value		<0.05	<0.05	<0.05

Rats were treated with natural Cordyceps (3 g/kg, i.p.) for the natural killer (NK) cell activity experiment, and with 5 g/kg, i.p. for the lung tumor development experiment for 3 days.

Data are adapted from Xu and Peng (1988) and are expressed as fractions of controls.

TABLE 31. EFFECTS OF NATURAL CORDYCEPS ON T-LYMPHOCYTE SUBGROUPS

		Lymphocytes in peripheral blood			
	n	*Total*	*T-helper*	*T-suppressor*	*Ratio of T_H:T_S*
Control	12	1.00 ± 0.15	1.00 ± 0.27	1.00 ± 0.16	1.00 ± 0.23
Cordyceps	12	1.32 ± 0.17	1.54 ± 0.29	1.09 ± 0.21	1.45 ± 0.30
p value		<0.001	<0.001	>0.05	<0.05

			Lymphocytes in spleen			
	n	*Spleen weight*	*Total*	*T_H*	*T_S*	*Ratio of T_H:T_S*
Control	12	1.00 ± 0.12	1.00 ± 0.02	1.00 ± 0.19	1.00 ± 0.18	1.00 ± 0.28
Cordyceps	12	1.57 ± 0.20	1.14 ± 0.12	1.24 ± 0.22	0.95 ± 0.16	1.27 ± 0.33
p value		<0.001	<0.05	<0.05	>0.05	<0.05

Mice were treated with either placebo or natural Cordyceps at a dose of 0.2 g/day, i.p. for 3 days. Peripheral blood samples were collected and the spleen was recovered at the end of experiment for analysis of lymphocytes.

T_H, T-helper lymphocytes; T_S, T-suppressor lymphocytes.

Data are adapted from Chen et al. (1987).

TABLE 32. DOSE-DEPENDENT INCREASES IN EXPRESSION OF INTERLEUKIN-1, INTERFERON, AND TUMOR NECROSIS FACTOR IN KUPFFER'S CELLS AFTER NATURAL CORDYCEPS TREATMENT

		Dose (g/kg)			
	n	*0 (control)*	*2*	*6*	*10*
IL-1	7	1.00 ± 0.32	2.00 ± 0.04	3.02 ± 0.39	2.15 ± 0.32
IFN	7	1.00 ± 0.80	3.35 ± 0.95	5.65 ± 1.90	4.65 ± 2.50
TNF (μg/mL)	7	0.00 ± 0.0	0.04 ± 0.04	0.13 ± 0.07	0.15 ± 0.08

Rats were administered natural Cordyceps at the doses indicated. Serum was prepared from the rats and used for *in vitro* analyses of interleukin-1 (IL-1), interferon (IFN), and tumor necrosis factor (TNF) production. Data for IL-1 and IFN are expressed as fractions of mean values for untreated controls, while the original data for TNF were listed.

Data are adapted from Liu et al. (1996).

CANCER TREATMENT

As previously reviewed in this article, Cordyceps and its mycelial fermentation products appear to function in many systems. They have shown beneficial effects in cancer patients and are used as adjuvant treatments for cancer. Cancer patients may benefit from an adjuvant therapy with Cordyceps through the enhancement of cell-mediated immunity, oxygen free radical scavenging, and augmentation of the cellular bioenergy system as described above. In addition, synergistic effects of Cordyceps with certain chemotherapy agents have been explored in animal studies. Water extracts of natural Cordyceps (10 g/kg, p.o.) and its

TABLE 33. INCREASED EXPRESSION OF INTERLEUKIN-2 RECEPTOR ON SURFACE OF PERIPHERAL LYMPHOCYTES DERIVED FROM PATIENTS AFTER TREATMENT WITH NATURAL CORDYCEPS

		IL-2 receptor		
	n	*Pretreatment*	*Post-treatment*	p *value*
Normal	13	1.00 ± 0.36	2.57 ± 1.54	<0.01
Nephritis	13	1.16 ± 0.47	2.86 ± 0.85	<0.01
Renal failure	12	0.56 ± 0.42	1.25 ± 0.61	<0.01

Peripheral blood samples were collected from normal individuals and patients with nephritis or chronic renal failure. Lymphocytes were isolated, cultured for 24 hours with or without natural Cordyceps, and analyzed for interleukin-2 (IL-2) receptors.

Data are adapted from Chen and Liu (1992).

mycelial fermentation products (5 g/kg, p.o.) were capable of enhancing the anticancer effects of cyclophosphamide, 6MP, or vincristine (Du et al., 1986; Xu et al., 1988). Direct exposure of cultured tumor cells to Cordyceps produced inhibition of growth and colony formation of the Hep-2 laryngeal carcinoma line, which appeared to be dose-dependent (Liu and Zheng, 1993). This suggests that Cordyceps may act directly against tumor cells, rather than the activity being mediated exclusively by actions of the host immune system.

In humans, continuous administration of Cs-4 was used as a supplementary treatment for terminal stage lung cancers, in combination with radiation therapy and chemotherapy (Cheng et al., 1995). Significantly more patients achieved greater tolerance to and were able to complete radiation therapy and/or chemotherapy for their lung cancer after addition of Cs-4 into their treatment regimen than those in the control group who received radiation therapy or chemotherapy alone (Table 36). More patients in the Cs-4 group showed blood counts within the normal range after radiation and/or chemotherapy than patients in the control group. These results indicated some effects of Cs-4 in improving tolerance to radiation therapy and/or chemotherapy, and minimizing bone marrow impairment due to such therapies.

XinGanBao capsule was used in combination with chemotherapy or other herbal treatments in a clinical trial treating 50 lung cancer patients (Yan et al., 1992b). After the treatment, subjective symptoms were improved in the majority of patients and tumor size, a product of horizontal and vertical dimensions, was partially or slightly reduced in 46% of the patients (Table 37). However, immunologic parameters did not change significantly. Another clinical trial was conducted with Zhiling capsule (a mycelial fermentation product of Cordyceps) in the treatment of patients with malignancies (Zhang et al., 1986). Subjective symptoms improved in nearly all the patients. Again, no patients showed white blood cell counts of less than $3000/mm^3$ after Zhiling capsule was used during radiation or chemotherapy, and about half the patients had their tumor size greatly reduced. And, again, immunologic parameters showed no significant change.

TABLE 34. CHANGES IN EXPRESSION OF SURFACE MOLECULES OF LYMPHOCYTES IN THYMUS OF RATS AFTER TREATMENT WITH A CORDYCEPS-DERIVED POLYSACCHARIDE

		CD_4^+/CD_8^+	CD_4^+/CD_8^-
Control	6	1.00 ± 0.04	1.00 ± 0.35
Cordyceps polysaccharide	6	0.61 ± 0.29	2.26 ± 1.00
p value		<0.01	<0.05

Rats were administered a polysaccharide derived from natural Cordyceps (100 mg/kg/day, i.p.) for 5 days. Thymus and spleen were used for analyses of expression of surface molecules of lymphocytes.

Data are adapted from Shen et al. (1991).

TABLE 35. CHANGES IN T LYMPHOCYTE SUBSETS IN PATIENTS WITH CHRONIC RENAL FAILURE AFTER NATURAL CORDYCEPS TREATMENT

		OKT_4		
	n	*Pretreatment*	*Post-treatment*	p *value*
Normal control	30	1.00 ± 0.14		
CRF	28	0.80 ± 0.13	0.90 ± 0.11	<0.05
		Ratio of $OKT_4:OKT_8$		
		Pretreatment	*Post-treatment*	
Normal control	30	1.00 ± 0.13		
CRF	28	0.81 ± 0.20	0.94 ± 0.13	<0.05

Patients with chronic renal failure (CRF) were administered natural Cordyceps (3–5 g/day) for 10 to 12 months.

Data are adapted from Guan et al. (1992) and expressed as fractions of mean values of normal controls.

TABLE 36. IMPROVED CLINICAL OUTCOMES IN LUNG CANCER PATIENTS TREATED WITH CS-4

		Completion of radiation/chemotherapy	*Normal blood counts after radiation/chemotherapy*
Control	39	25 (64%)	23 (59%)
Cs-4	20	19 (95%)	17 (85%)
p value		<0.01	<0.01

Patients with terminal stage lung cancer were continuously administered Cs-4 (2–3 g/day) in conjunction with radiation and/or chemotherapy.
Data are adapted from Cheng et al. (1995).

INHIBITORY EFFECTS ON THE NERVOUS SYSTEM

It has been reported that Cordyceps affects the central and peripheral nervous system. In animals, Cs-4 inhibited autonomic movements of muscles (Bao et al., 1988). In rats administered an ethanol extract of Cs-4 (5, 10, 20 g/kg, s.c.), autonomic movements were significantly reduced by over 70% compared to controls ($p <$ 0.001). High-dose Cs-4 treatment significantly reduced body temperature from 38.2° ± 0.1°C in controls to 37.4° ± 0.2°C (Cs-4 10 g/kg) or to 35.9° ± 0.3°C (Cs-4 20 g/kg) and pilocarpine (5 mg/kg, i.v.)-induced salivation, as compared to controls ($p < 0.05$ to < 0.001). In rats given pentobarbital (45 mg/kg, i.p.) plus Cs-4 (10 or 20 mg/kg), the sleeping time was significantly prolonged (+49% or +64%) as compared to placebo controls ($p < 0.05$ and < 0.01). Similar results showing decreased autonomic movements have been reported by others (Wang and Zhao, 1987) when natural Cordyceps was used. These experiments indicate that natural Cordyceps and its mycelial fermentation products have inhibitory and sedative effects on nervous systems, in both the central and peripheral nervous system.

ANTI-INFLAMMATORY ACTIVITY

Preclinical experiments indicate that Cordyceps may be effective against inflammatory conditions. After groups of mice were administered different dosages of Cs-4 extract (equivalent to original powder, 5 to 20 g/kg, subcutaneously), croton oil-induced inflammation of the ear area was significantly inhibited, represented by significantly reduced ear weight (Bao et al., 1988). The effect was clearly dose-dependent, −22% in 5 g/kg group, −35% in 10 g/kg group, and −50% in 20 g/kg group compared to the placebo control group ($p < 0.01$ to < 0.001). Similar results were also obtained when natural Cordyceps or another mycelial fermentation product (*Cephalosporium sinensis*) was administered to animals (Wang and Zhao, 1987). Mice with dimethylbenzene-induced local inflammation of the ears was treated with either of the two Cordyceps preparations. Ear weight was significantly lower than that observed in controls.

Anti-inflammatory effects of Cordyceps were also tested in a rat model with claw inflammation induced by raw egg white (Wang and Zhao, 1987). Rats were administrated (intravenously) either placebo, natural Cordyceps

TABLE 37. REDUCTION OF TUMOR SIZE IN LUNG CANCER PATIENTS TREATED WITH CS-4

n	*All symptoms improved*	*Tumor completely disappeared*	*Reduction in size of tumor*			*Tumor enlarged*
			>50%	*>25%, <50%*	*<25%, no change*	
50	68%–100%	2 (4%)	6 (12%)	15 (30%)	9 (18%)	1 (2%)

Patients with lung cancer were continuously administered XinGanBao (6 g/day) for more than 2 months in conjunction with other traditional Chinese herbs (individualized herbal formulas) and/or radiation therapy.
Data are adapted from Yan et al. (1992).

TABLE 38. ACUTE TOXICITY STUDIES OF NATURAL CORDYCEPS AND ITS MYCELIAL FERMENTATION PRODUCTS

	Cordyceps	*Cs-4*	Cephalosporium sinensis
Deaths	0	0	0
LD_{50}	Not detectable	Not detectable	Not detectable

Mice were administered Cordyceps or its mycelial fermentation products at 80 g/kg, p.o., and observed for 7 days or longer.

LD_{50}, median lethal dose.

Data are adapted from Xia et al. (1985); Wang and Zhao (1987); Xu (1992); and Institute of Materia Medica. Clinical application of fermented Cordyceps sinensis Cs-4 (Part III): Toxicology. Unpublished report, 1996.

(3.1 g/kg), or hydrocortisone (20 mg/kg). Thirty minutes later, they received a local injection of egg white to the claw and were then examined at 1, 3, and 6 hours. An anti-inflammatory effect, represented by reduced volume of claw by over 30% was clearly evident, and lasted longer than 6 hours.

The mechanisms of these anti-inflammatory effects of Cordyceps have yet to be elucidated. Although so far there have been no clinical reports on the use of Cordyceps against joint or skin inflammation, the anti-inflammatory activity may benefit patients with inflammatory diseases of the respiratory system, such as chronic bronchitis, or other conditions for which Cordyceps is traditionally regarded efficacious.

SAFETY

In general, Cordyceps is reported to be a very safe, traditional Chinese herb. Indeed, many investigators have reported that an oral LD_{50} (median lethal dose) of Cordyceps and its mycelial fermentation products could not be detected. For instance, no deaths were seen 7 days or longer after mice were administered Cordyceps, Cs-4, or *Cephalosporium sinensis* at an oral dosage of 80 g/kg (Table 38) (Wang and Zhao, 1987; Xu, 1992; Institute of Materia Medica. Clinical application of fermented *Cordyceps sinensis* Cs-4 (Part III): Toxicology. Unpublished report, 1996).

Mutagenicity and teratogenicity studies of Cs-4, *Cephalosporium sinensis*, or Cordyceps

TABLE 39. EFFECTS OF CULTURED MYCELIA (*CEPHALOSPORIUM SINENSIS*) OF CORDYCEPS ON THE REPRODUCTIVITY OF WISTAR RATS AND GROWTH AND DEVELOPMENT OF RAT EMBRYOS.

				Embryos				
	Dose (g/kg)	*Pregnant rats (n)*	*Implanted (n)*	*Absorbed (n)*	*Death (n)*	*Body weight (g)*	*Body length (cm)*	*Tail length (cm)*
Control		11	121	0	1	4.1 ± 0.4	4.0 ± 0.1	1.5 ± 0.1
Cephalosporium	1.25	11	128	2	0	4.0 ± 0.7	4.0 ± 0.1	1.5 ± 0.1
Cephalosporium	2.5	11	118	0	0	4.1 ± 0.6	4.0 ± 0.2	1.4 ± 0.1
Cephalosporium	5.0	11	112	0	0	3.9 ± 0.2	3.9 ± 0.2	1.4 ± 0.1

			No. of embryos with delayed bone development (%)		
	Dose (g/kg)	*Embryo (n)*	*Os incae*	*Occiput*	*Sternum*
Control		64	2 (3.1%)	4 (6.2%)	7 (10.0%)
Cephalosporium	1.25	67	1 (1.4%)	2 (2.9%)	7 (10.4%)
Cephalosporium	2.5	62	3 (4.8%)	2 (3.2%)	4 (6.4%)
Cephalosporium	5.0	58	0 (0.0%)	2 (3.4%)	3 (5.1%)

Virgin female Wistar rats were kept with male rats and administered orally a mycelial fermentation product (*Cephalosporium sinensis*) at the doses indicated for 10 days starting at day 6 of pregnancy. Their pregnancy and the development and condition of embryos were examined at day 21.

Data are adapted from Jing et al. (1987).

TABLE 40. *IN VIVO* MUTAGENICITY OF A CORDYCEPS MYCELIAL FERMENTATION PRODUCT (Cs-B_{414}) IN RABBITS

	Lymphocytes examined	*Micronucleated peripheral lymphocytes (%)*	
		Pretreatment	*Post-treatment*
Placebo	10000	1.00 ± 0.02	1.10 ± 0.19
Cs-B_{414}	16000	1.06 ± 0.15	1.00 ± 0.13

Rabbits were administered placebo or a Cordyceps mycelial fermentation product (Cs-B_{414}) for 3 months.
Data are adapted from Huang et al. (1987).

mycelia Cs-B_{414} demonstrated negative results in *Salmonella typhimurium* strains by the Ames test and in animal studies for teratogenic and mutagenic activities (Tables 38–40) (Jing et al., 1987; Huang et al., 1987; Xu, 1992). These results indicate that Cordyceps and its mycelial fermentation products are not mutagenic or teratogenic.

In subacute toxicity studies, Cs-4 was administered orally to mice for 30 days (Wan, Zhang. Clinical observations of fermented *Cordyceps sinensis* (Cs-4) in antitussive, expectorant, and antathematic effects. Unpublished report, Jiangxi Institute of Medical Sciences, pp. 35–39) or to rats for 3 months (Institute of Materia Medica. Clinical application of fermented *Cordyceps sinensis* Cs-4 (Part III): Toxicology. Unpublished report, 1996), while placebo was given to the control animals. No deaths were observed at the end of either study. The animals in the experimental groups and the control group showed no differences in relative organ weights and blood counts (CBCs), and appeared to have similar increases in body weight (Table 41). Although there may have been an initial delay in the growth of the animals due to initial displeasure at the unfamiliar odor of the Cs-4-containing forage, rats in the high-dose group grew faster in the later phases of the experiment. Microscopic examinations after the feeding periods revealed no differences in any of the organs from the mice or rats from all groups. Increasing the dosage caused no significant changes in body weight increase and the histology of organs in either male or female rats after the treatment showed no differences compared to the placebo controls (Institute of Materia Medica. Clinical application of fermented *Cordyceps sinensis* Cs-4 (Part III): Toxicology. Unpublished report, 1996).

TABLE 41. EXAMINATIONS OF PERIPHERAL BLOOD CELLS OF RATS AFTER Cs-4 TREATMENT FOR 3 MONTHS

	n	*Dose (g/kg)*	*Hemoglobin (g)*	*WBC ($\times 10^{-4}$)*	*Lymphocytes (%)*	*Neutrophils (%)*
Control	20		14.6 ± 1.1	1.20 ± 0.2	73.4 ± 4.5	23.4 ± 5.5
Cs-4	20	3.0	13.9 ± 1.1	1.00 ± 0.1	70.8 ± 8.3	26.4 ± 8.7

			Organ weight (relative to body weight)					
	n	*Dose (g/kg)*	*Heart*	*Liver*	*Kidney*	*Lung*	*Spleen*	*Testes*
Control	20		3.5 ± 0.5	36.8 ± 2.7	6.7 ± 1.1	8.1 ± 3.1	3.3 ± 1.5	10.4 ± 1.8
Cs-4	20	3.0	3.5 ± 0.5	37.2 ± 3.4	6.1 ± 0.8	9.0 ± 3.2	3.0 ± 2.0	9.70 ± 0.6

			Average body weight (g)					
	n	*Dose (g/kg)*	*Pre*	*At 1 week*	*At 2 weeks*	*At 4 weeks*	*At 8 weeks*	*At 13 weeks*
Female rats								
Control	4		78.2	120	151	186	250	265
Cs-4	4	5	79.8	117	151	194	255	283
Cs-4	4	20	77.2	103	120	192	245	269
Male rats								
Control	5		80.2	122	156	243	332	369
Cs-4	5	5	82.8	116	159	249	346	386
Cs-4	4	20	82.8	109	127	209	298	348

Rats were administered placebo or Cs-4 for 3 months at the doses indicated.
WBC, white blood cell counts.
Data are adapted from an unpublished report by the Institute of Materia Medica, Beijing (1996).

TABLE 42. EFFECTS OF 3-MONTH Cs-4 TREATMENT ON LIVER AND RENAL FUNCTIONS IN DOGS

	n	Dose (g/kg)	Hemoglobin (g)	WBC ($\times 10^{-4}$)	Lymphocytes (%)	Neutrophils (%)
Control	4		15.5 ± 0.3	1.20 ± 0.1	34.5 ± 4.0	63.7 ± 4.1
Cs-4	4	3.0	15.3 ± 0.8	1.20 ± 0.2	33.5 ± 3.9	65.0 ± 4.5

	n	Dose (g/kg)	GPT (U/L)		BUN (mg/dL)	
			At 1.5 months	At 3 months	At 1.5 months	At 3 months
Control	4		91.3 ± 24.3	50.0 ± 12.9	6.7 ± 2.0	10.4 ± 2.1
Cs-4	4	3.0	98.7 ± 40.5	61.0 ± 28.2	7.5 ± 0.6	7.90 ± 1.8

Dogs were administered orally placebo or Cs-4 for 3 months at a dose of 3 g/kg.
WBC, white blood cell counts; GPT, glutamic-pyruvic transaminase; BUN, blood urea nitrogen.
Data are adapted from an unpublished report by the Institute of Materia Medica, Beijing (1996).

In dogs treated with Cs-4 for 3 months, no differences were found in CBCs, SGPT, TTT, or BUN compared to placebo controls (Table 42) (Institute of Materia Medica. Clinical application of fermented *Cordyceps sinensis* Cs-4 (Part III): Toxicology. Unpublished report, 1996). Finally, microscopic examinations after the feeding period with Cs-4 at high daily doses showed no differences as compared to placebo controls.

In another subchronic toxicity study, Cs-B_{414} (10 g/kg) was administrated orally to rabbits ($n = 6$) for 3 months, (Huang et al., 1987) while placebo was given to the control animals ($n = 5$). No deaths were observed at the end of the study. The animals in the two groups showed no differences in heart rate, body temperature, eating habits, bowel movements, and general physical conditions. Rabbits in the treatment group appeared to gain more weight at the end of the study: 18.5% higher than the placebo controls ($p < 0.05$). The mechanisms for the faster growth have yet to be elucidated. There were no differences in blood counts, SGPT, and BUN between the two groups. Pathological examinations after the feeding periods revealed no differences in the organs of the rabbits from the two groups, except for an increase in the weight of testes in the treatment group (Huang et al., 1987). The increased testes weight was associated with a significant increase in the sperm count, yet with a normal microscopic structure of the testes, as stated earlier. Histological examinations for all other organs revealed no apparent structural differences.

From clinical studies, there are reports of mild upper gastrointestinal discomforts, such as nausea, dry mouth, and stomach discomfort in some patients taking Cs-4 (Xu, 1992). There is one report of one patient who developed a systemic allergic reaction after taking Cs-4 (Xu, 1994). However, all the investigators reported that, in their opinion, Cordyceps and its mycelial fermentation products are very safe during clinical use.

DISCUSSION

We have attempted to review all significant animal and human studies conducted, using characterized natural and fermented Cordyceps and their extracts. Our selection was done the "Western way," using scientific criteria, and we did not consider studies performed strictly according to the tradition and philosophy of "traditional Chinese medicine."

We shall first attempt to summarize the results of these studies by categorizing their conclusions.

a. Considering physical performance, Cordyceps intake was associated with an overall improvement in humans. Probably due to its activities of improving the energy-state in cells and of scavenging oxygen free radicals to reduce oxidative stress, Cordyceps reduced fatigue, intolerance to cold, dizziness, tinnitus, and memory loss, while increasing respiratory capacity. Thus, clinical

use of Cordyceps was strongly associated with an improvement in the quality of life.

b. Traditionally, Cordyceps has been widely used to stimulate libido. Indeed, treatments with Cordyceps were associated with an increase of libido in both males and females, increased synthesis of 17-OH corticosteroids and 17-ketosteroids. There was also a massive reduction in the number of abnormal spermatozoa. These clinical results were confirmed in mice, rats, and rabbits, with a significant increase in the volume and weight of the sexual organs.

c. Lipid metabolisms affected by Cordyceps: After 30 days of treatment, triglycerides and total cholesterol were significantly lowered. Most interestingly, high-density lipoprotein cholesterol was dramatically increased by about 30% after treatment.

d. The respiratory tract has been a traditional target of Cordyceps. In animals, Cordyceps increases respiratory secretions to facilitate expectoration, while calming cough. It seems to be an anti-asthmatic in guinea pigs. Several clinical studies have confirmed its beneficial effects in patients with chronic bronchitis, bronchial asthma, and cor pulmonale, with improvement of pulmonary function. In patients with a cough as an equivalent of asthma, Cordyceps provided better, faster relief.

e. Cordyceps is also a medicine taken for the kidneys. It helped improve renal functions in patients with renal dysfunction, decrease BUN and creatinine, and correct anemia. Hypertension was easier to control. An increase in SOD was reported. Another series of clinical studies confirmed the protective role of Cordyceps against kidney toxicity associated with aminoglycoside antibiotics (kanamycin, amikacin, gentamicin), or cyclosporin A.

f. Cardiovascular benefits are strongly supported: control of most arrhythmias, with ECG confirmation; major improvement of ECG and clinical symptoms in patients with ischemic heart disease or chronic heart failure; and decrease of anoxia of the heart. Blood and plasma viscosity were reduced and ECG was improved. Comparable to effects reported with *Ginkgo biloba* (Halpern, 1998), Cordyceps improves blood circulation to essential organs, such as the heart and brain, decreases platelet aggregation, and prevents thrombosis.

g. Patients with liver problems were successfully treated with Cordyceps: in some patients with hepatitis B, turbidity blood tests returned to normal; the same results were observed in patients with post-hepatitis cirrhosis. Cordyceps induced a major reduction of the hepatitis B viral load. Clinical improvement was also observed in patients with post-schistosomiasis cirrhosis.

h. Cordyceps appeared to be a hypoglycemic agent in animals, independent of insulin. The activity involves various enzymes (hexokinase, glucose-6-phosphate dehydrogenase, hepatic glucokinase); Cordyceps helped diabetic patients control their glucose metabolism. Cordyceps may have a mechanism of action similar to the one(s) of metformin.

i. Cordyceps is a moderate immunomodulator. Cordyceps exhibits one or more of those inhibitory and stimulatory functions in immune systems under different experimental conditions. Some of the immune effects observed, including an increase in the production of IFN, may be similar to those of bacterial extracts or of mushrooms (Halpern, 1977; Halpern et al., 1992, 1993; Hobbs, 1995).

j. In patients with malignancies, Codyceps was synergistic with some chemotherapeutic agents. It significantly improved tolerance to radiation and chemotherapy.

k. In animals, Cordyceps affected some impairment of the central nervous system: reduction of autonomic movements and an increase in the effects of sedatives.

l. Also in animals, anti-inflammatory activity was demonstrated.

m. Finally, all preparations of Cordyceps used in these studies proved to be extremely safe, even at very high doses and after prolonged use. We found only one report of an allergic reaction possibly associated with Cordyceps.

Where do we go from here? As stated, we chose the "Western" scientific approach, and are perplexed by the scale and spectrum of ac-

tivities of Cordyceps. Further identifying and characterizing the active components of Cordyceps preparations and elucidating their activities are needed. We should also consider a number of interactions with enzymes, various receptors in diverse organs, and the many unknown or unexplored variables of individual patients. The multidimensional characterization of some of these components should help in our synthetic approach to place Cordyceps in the therapeutical armamentarium.

Cordyceps is a TCM herb. It has also been used for centuries as a food, albeit a rare, expensive one. But some culinary recommendations, as listed in Part I, Table 2 (Zhu et al., 1998), point to a major role of the diet associated with Cordyceps treatments. We could not find any information on the patients' diets in the clinical studies cited. In addition to the diet, the genetic and environmental background must play a role, and is very different from the one we would study elsewhere. We believe these are important caveats. The life cycle of Cordyceps also strikes the imagination; in ancient times it attained the fantastic, and must have been associated with some persisting magical beliefs, at least in the unblinded control groups. We are just beginning to explore the mind-body relations, the actions of brain chemicals on peripheral organs, and the triangular relationship of central nervous system-endocrine-immune systems. Cordyceps is already a symbol of incredible potential for survival and resilience, and may well be a symbol of life.

ACKNOWLEDGMENTS

The authors are grateful to Professors Michael Zhu, Xingkai Lui, and Deji Pan, Dr. Janny Ju, and Mr. Jacky Cao, Shanghai Medical University, for their assistance. The authors thank Professor Tiantong Bao, Institute of Materia Medica, Chinese Academy of Medical Sciences, for his scientific discussion. The authors also thank the generously granted permissions for republishing the photographs of natural Cordyceps from Mr. Xiu-Zhang Chen, editor of the Fujian Science and Technology publication; Mr. Lo Hsien Shui, editor of the Guangdong Science and Technology publication; and Mrs. Zhao Su-Yun, Beijing People's Health Press.

ADDENDUM

In Part I of this review, we examined studies indicating that Cordyceps improves endurance and the quality of life of patients. A recent double-blind, placebo-controlled clinical trial in healthy elderly subjects ($n = 30$, 50 to 75 years old) revealed that Cs-4 significantly improved the volume of maximal oxygen intake (an average 6.4% increase, $p = 0.05$) during a submaximal exercise test after a 6-week treatment (Xiao, Huang, Chen, Wang, Zhu, and Cooper, manuscript in preparation, Peking Union Medical University and the University of California, Los Angeles). In addition, there was a marked increase in METs (an average 8.6% increase; $p = 0.038$), indicating enhanced muscle metabolism-exercise capability. The results suggest improvement of respiratory-cardiovascular functions and quality of life in the elderly subjects following Cs-4 treatment.

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