CordyMax™ Studies Compendium

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CordyMax Cs-4 Healthcare Professional Product Guide
The following abstract was presented at the 48th Annual Meeting of the American College of Sports Medicine held in Baltimore, MD, May 30-June 2, 2001. The abstract was published in *Medicine & Science in Sports & Exercise* the official journal of the American College of Sports Medicine (full citation below). A full-length article is not available. With a paid subscription this same abstract can be viewed at:


When you have accessed the above webpage, scroll to S164, or simply conduct a Ctrl+F search for “Cordyceps Cs-4”.

**Publication Reference:**

\(^1\)Fit Stop Human Performance Laboratory, Encinitas, CA.
\(^2\)Pharmanex Research Institute.

**Cordyceps preparation used by Nicodemus et al. in their 2001 publication:** CordyMax\(^{Cs-4}\) [Pharmanex (Provo, UT)]

Supplementation with Cordyceps Cs-4 fermentation product promotes fat metabolism during prolonged exercise.

**ABSTRACT**

In a preliminary report, six weeks of supplementation with a natural fermentation product of a specific strain of *Cordyceps sinensis* (Cs-4, CordyMax™) was associated with increases in peak oxygen uptake (VO\(_{2}\)peak) and anaerobic threshold in older humans (>57 yr) (*Med. Sci. Sports Exerc.*, 1999;31(5):S174). We conducted a randomized, double-blind study, to further determine the effect of six wks of the daily intake (4.5 gm•day\(^{-1}\)) of Cs-4 in highly-fit athletes on oxygen uptake (VO\(_{2}\)), carbon dioxide production (VCO\(_{2}\)), ventilatory threshold (VT), and heart rate (HR) during maximal and submaximal treadmill exercise. Thirty male adventure racers and multi-sport endurance athletes (31.8 ± 4.3 yrs, VO\(_{2}\)peak of 62.6 ± 7.7 ml•kg\(^{-1}\)•min\(^{-1}\)) were assigned to either a Cs-4 or a placebo control (CON) group (n=15 each). Before and after the supplementation period, each subject performed a maximal treadmill test using a running protocol, followed the next day by a submaximal running test (60 min at 70% VO\(_{2}\)peak). VO\(_{2}\), VCO\(_{2}\), and HR were measured throughout maximal exercise and during 15 min of recovery; they and blood lactate (LA) were also examined every 15\(^{th}\) min during and 5-min after the submaximal test. Post-test peak VO\(_{2}\) and VT were significantly higher for Cs-4 and CON compared to pre-test values, but the difference between the groups was non-significant. Post-test submaximal exercise HR was 2.2% lower for Cs-4 compared to pre-test values (p=0.056), but the difference between the groups was non-significant (p range = 0.1-0.2). MANOVA on the submaximal exercise post-test and pre-test difference scores showed increases in oxygen pulse (+7.6%, p=0.058), and decreases in respiratory exchange ratio at all time points (-1.9% to -3.3%, p=0.02 to 0.05) and LA at the 30\(^{th}\) min (-1.5%, p=0.038) for Cs-4 after the supplementation compared to CON. Our findings suggest that Cs-4 supplementation may have positive circulatory and metabolic effects during submaximal exercise in endurance-conditioned athletes. Cs-4 may enhance fat mobilization and beta-oxidation, thereby sparing glycogen usage during prolonged exercise.

Supported by Pharmanex, Inc., Brisbane, CA
The following study was presented at the Experimental Biology (FASEB) meeting in New Orleans, Louisiana, April 20-24, 2002. A full-length study write-up is not available.
CordyMax Cs-4 improves cardiovascular and metabolic capacity during exercise in highly-fit athletes.

ABSTRACT

Previous studies indicated CordyMax Cs-4 (Cs), a mycelia fermentation product of Cordyceps sinensis improved aerobic capacity in older humans and bio-energy metabolism in animals (Med. Sci Sports Exerc 1999; 31(5): S174 & S120). We tested the effect of Cs (4.5 g/day) on cardiovascular and metabolic capacity during peak (IWR) & submaximal (CWR: 60 min at 70% VO2peak) treadmill exercise. Male highly-fit athletes (age 32±4 yrs; VO2peak 63±8 ml/kg/min) were randomized to a Cs or a placebo group (n=15 each; double-blind). O2 uptake, CO2 output, and heart rate (HR) were measured throughout IWR test; they and blood lactate were examined every 15th minute during the CWR test. Six weeks of Cs prevented physical training induced increases in peak HR, increased peak O2 pulse (+7%, p=0.04) during IWR, and reduced HR (-2.2%, p=0.056) during RER exercise. Cs lowered basal blood glucose (-7%, p<0.01), and reduced RER (-3%, p=0.059) and blood lactate (-11%, p=0.03) during CWR exercise. These findings indicate CordyMax improved cardiovascular and metabolic functions of the highly-fit athletes during exercise, favoring more robust physical conditions.

Supported by a clinical grant from Pharmanex, Provo, UT.
The following abstract was presented at the Experimental Biology (FASEB) meeting in Orlando, Florida, March 31-April 4, 2001. A full-length study write-up is not available.

**Publication reference:**

Pharmanex, Brisbane, CA and Fit Stop Human Performance Laboratory, Encinitas, CA.

**Cordyceps preparation used by Zhu et al. in their 2001 study:** CordyMax™ Cs-4 [Pharmanex (Provo, UT)]

### CordyMax™ Cs-4 Improves Glucose Metabolism

**ABSTRACT**

Preliminary reports demonstrated that 6-wks treatment of a natural fermentation product of a specific mycelial strain of *Cordyceps sinensis* (CordyMax™ Cs-4) increased maximal $\text{O}_2$ uptake and anaerobic threshold in older humans (>57 yr), and enhanced in vivo bio-energy metabolisms in animals (Med. Sci, Sports Exerc. 1999; 31(5): S174 & S120). We further studied in a randomized, double-blind clinical trial the effect of Cs-4 (4.5 g/day, 6 wks) in highly-fit athletes on glucose (Glu) metabolism. Male adventure racers and multi-sport endurance athletes (age 32±4 yrs; $\text{VO}_2^{\text{peak}}$ 63±8 ml/kg/min) were assigned to either a Cs-4 or a control group (n=15 each). We found 7% decrease within normal ranges in fast blood Glu after the Cs-4 therapy (92±1 to 87±2 mg/dL: p<0.01), but no change in placebo controls. During prolonged sub-maximal exercise (70% $\text{VO}_2^{\text{peak}}$, 60 min), reductions of respiratory exchange ratio were found in the Cs-4 vs. control group (p=0.02). In mice given Cs-4 for 4 wks, responses of serum insulin and C-peptide to an oral Glu load were diminished and recovered quickly vs. control group (p<0.01 or 0.05) with no change in the Glu tolerant curve. The Glu-insulin index was lower in the Cs-4 (7±1 x10⁵ units) vs. control group (10±1 x10⁵) (p<0.01). Our data suggest that Cs-4 (1) safely lowers basal glucose in normal humans, (2) improves glucose metabolism by enhancing insulin receptor sensitivity, and (3) enhances fat mobilization and beta-oxidation thereby sparing glycogen expenditure during prolonged submaximal exercise.
The following abstract was presented at the 46th Annual Meeting of the American College of Sports Medicine held in Seattle, WA, June 2-5, 1999. The abstract was published in *Medicine & Science in Sports & Exercise*, the official journal of the American College of Sports Medicine (full citation below). With subscription this same abstract can be viewed at:


When you have accessed the above webpage, scroll to S174, or simply conduct a Ctrl+F search for “Cordyceps Cs-4”.

**Publication Reference:**

**Cordyceps preparation used by Xiao et al. in their 1999 publication:** CordyMax™ [Pharmanex (Provo, UT)]

Increased aerobic capacity in healthy elderly humans given a fermentation product of Cordyceps Cs-4.

**ABSTRACT**

*Cordyceps sinensis* is a natural herbal medicine, popular in China as a dietary supplement for invigoration, health preservation and reducing fatigue. The natural substance has been refined as a fermentation product of a specific strain of *Cordyceps sinensis* (Cs-4; CordyMax™). Our objective was to test the effect of Cs-4 on exercise capacity in a double-blind, placebo-controlled trial. Thirty healthy, elderly Chinese subjects were randomly assigned to receive either Cs-4 (3g/day) or identical placebo capsules. Exercise performance was tested before and after 6 weeks of treatment using a symptom-limited, incremental work rate protocol on a cycle ergometer. Maximum oxygen uptake (VO$_2$max) was measured using a metabolic cart. Anaerobic thresholds (VO$_2$θ) were identified by two observers using plots of both VCO$_2$ versus VO$_2$ and V$_{EQ}$O$_2$ versus time. The results were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Cs-4</th>
<th>Cs-4</th>
<th>PLACEBO</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
</tr>
<tr>
<td>n(M:F)</td>
<td>16 (10:6)</td>
<td>14 (8:6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (1)</td>
<td>66 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W$_{max}$ (watt)</td>
<td>123 (7)</td>
<td>128 (6)</td>
<td>123 (11)</td>
<td>118 (9)</td>
</tr>
<tr>
<td>VO$_2$max (L/min)</td>
<td>1.88 (0.13)</td>
<td>2.00 (0.14)</td>
<td>1.80 (0.12)</td>
<td>1.79 (0.11)</td>
</tr>
<tr>
<td>VO$_2$max (ml/kg/min)</td>
<td>27 (2)</td>
<td>29 (2)</td>
<td>28 (1)</td>
<td>27 (1)</td>
</tr>
<tr>
<td>%predVO$_2$max</td>
<td>95 (5)</td>
<td>101 (5)</td>
<td>96 (6)</td>
<td>96 (6)</td>
</tr>
<tr>
<td>VO$_2$θ (L/min)</td>
<td>1.15 (0.07)</td>
<td>1.30 (0.09)**</td>
<td>1.20 (0.05)</td>
<td>1.18 (0.07)</td>
</tr>
<tr>
<td>VO$_2$θ/predVO$_2$max (%)</td>
<td>59 (3)</td>
<td>66 (4)**</td>
<td>65 (3)</td>
<td>63 (4)</td>
</tr>
</tbody>
</table>

Values are mean (SEM). Comparing pre and post: *P=0.05; **P=0.01

After taking Cs-4 for 6 weeks, VO$_2$max and VO$_2$θ were significantly increased, whereas after placebo they were unchanged. These findings support the belief, held in China, that Cs-4 has potential for improving exercise capacity and resistance to fatigue.

Supported by research grants from Pharmanex, Inc.
CordyMax Cs-4 Enhances Endurance in Sedentary Individuals.

ABSTRACT

Previous studies of dietary supplementation with CordyMax Cs-4 (Cs-4), a proprietary fermentation product of the *Cordyceps sinensis* mushroom, have demonstrated significant improvements in bioenergy status in animals (JACM 2001;7:231-240), maximal oxygen consumption (VO$_2$max) in frail elderly subjects (MSSE 1999;31:S174) and exercise performance (HR, Lactate, RER) in elite endurance athletes (MSSE 2001;33:S164). The aim of this study was to investigate the effect of Cs-4 on endurance parameters in a population of healthy sedentary adults. Subjects were randomly assigned, in a double-blind fashion, to receive Cs-4 (n=55) or placebo (P, n=55) for 12 weeks. Measurements of VO$_2$peak, respiratory exchange ratio (RER), 1-mile walk time, and work output (Jeukendrup bike test), were performed at baseline and 12 weeks. VO$_2$peak increased 5.5% in Cs-4 (p = 0.003) but only 2.1% in P (NS). Exercise time to VO$_2$peak was longer in Cs-4 (5.4%, p=0.04), but not in P (2.2%, NS). RER was reduced 2.1% in Cs-4 (p=0.02), with no change in P. Time to complete a 1-mile walk was reduced by 20 sec in Cs-4 (p=0.05), but increased by 13 sec in P (NS). Work output (kJ/kg) on the bike test was increased by 2.8% in Cs-4 (p=0.03), but fell by 5.6% in P (NS). These data, collected in a population of healthy sedentary adults, confirm previous findings in animals, frail elderly subjects and elite athletes, showing a metabolic effect of Cs-4 supplementation to favorably influence oxygen consumption, energy metabolism and endurance performance. Further research is needed to determine the precise mechanism of action by which Cs-4 exerts these effects.

Supported by a grant from Pharmanex, LLC.
The following abstract was presented at the Experimental Biology (FASEB) meeting in Washington DC, April 17-21, 2004. A full-length study write-up is not available.

**Publication reference:**
Zhu JS¹, Rippe JM². CordyMax enhances aerobic Capability, Endurance Performance, and Exercise Metabolism in Healthy, Mid-age to Elderly Sedentary Humans. *FASEB J Meeting Abstracts*, 2004; 18(5): A931

¹Pharmanex Clinical Center, Pharmanex, LLC., 75 W. Center Street, Provo, UT 84601,  
²Clinical Research, Rippe Lifestyle Institute, Shrewsbury, MA

**Cordyceps preparation used by Zhu and Rippe in their 2004 publication:** CordyMax Cs-4 [Pharmanex (Provo, UT)]

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**CordyMax enhances aerobic exercise capacity and metabolism, and endurance performance in healthy, mid-age to elderly, sedentary humans.**

**ABSTRACT**

Previous studies of oral supplementation with CordyMax (CM), a proprietary mycelial fermentation product of the *Cordyceps sinensis*, have demonstrated significant improvements in aerobic capacity in older humans and in exercise performance and metabolism in elite athletes (JACM 2001;7:231; FASEB 2002;16:A628). This randomized, double-blind clinical study further examined the effect of CM on endurance parameters in healthy, sedentary adults. Subjects (40-70 yrs old) received either CM (n=61) or placebo (P; n=70) for 12 weeks. VO₂peak, respiratory exchange ratio (RER), time to complete a 1-mile walk (TMW), and work output (WO) by Jeukendrup bike test were examined at Weeks 0, 6, and 12. VO₂peak was increased by 5.5% in CM (p=0.003), but by only 2.2% in P (NS). Exercise time to VO₂peak was longer in CM (+5.4%, p=0.047), but no change in P. TMW was reduced by 29 sec in CM (p=0.05), but slightly increased in P (+19 sec, NS). WO was increased by 2.8% in CM (p=0.033), but fell in P (-5.6%, NS). RER was reduced by 2.1% in CM (p=0.018), but no change in P. Diastolic blood pressure was reduced by 3.2% in CM (p=0.045), but no change in P.

Consistent with previous findings in healthy, elderly and athlete individuals, these data indicates that oral CM supplementation improves aerobic capability, exercise metabolism, and endurance performance in healthy, mid-age to elderly sedentary humans.

Supported by a grant from Pharmanex.
The following study was published in the Journal of Alternative and Complementary Medicine on May 16, 2010.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110835/

**Publication reference:**

*Cordyceps preparation used by Chen et al. in their 2010 publication:* CordyMax<sup>Cs-4</sup> [Pharmanex (Provo, UT)]

Effect of Cs-4 (Cordyceps sinensis) on exercise performance in healthy older subjects: a double-blind, placebo-controlled trial.

**ABSTRACT**

**OBJECTIVE:** The objective of this study was to examine the effect of Cs-4 (Cordyceps sinensis) on exercise performance in healthy elderly subjects.

**DESIGN:** Twenty (20) healthy elderly (age 50-75 years) subjects were enrolled in this double-blind, placebo-controlled, prospective trial. The subjects were taking either Cs-4 333 mg or placebo capsules 3 times a day for 12 weeks.

**MEASUREMENT:** Subjects received baseline screening including physical examination and laboratory tests. Maximal incremental exercise testing was performed on a stationary cycle ergometer using breath-by-breath analysis at baseline and at the completion of the study.

**RESULTS:** After receiving Cs-4 for 12 weeks, the metabolic threshold (above which lactate accumulates) increased by 10.5% from 0.83 +/- 0.06 to 0.93 +/- 0.08 L/min (p < 0.02) and the ventilatory threshold (above which unbuffered H<sup>+</sup> stimulates ventilation) increased by 8.5% from 1.25 +/- 0.11 to 1.36 +/- 0.15 L/min. Significant changes in metabolic or ventilatory threshold were not seen for the subjects in the placebo group after 12 weeks, and there were no changes in V<sub>o</sub>(2) max in either group.

**CONCLUSION:** This pilot study suggests that supplementation with Cs-4 (Cordyceps sinensis) improves exercise performance and might contribute to wellness in healthy older subjects.
The following abstract was presented at the American Heart Association’s Scientific Sessions in Orlando, FL. November 9-12, 2003. The abstract was published in Circulation, the official journal of the American Heart Association. No online abstract is available.

Publication reference:

Cordyceps preparation used by Zhu et al. in their 2003 publication: CordyMaxCs4 [Pharmanex (Provo, UT)]

CordyMax reduces serum oxidized LDL-cholesterol and increases HDL-cholesterol in humans with reduced HDL-cholesterol

ABSTRACT

Literature reported that CordyMax (Cs4), a mycelial fermentation product of Cordyceps sinensis, regulated serum lipids in hyperlipidemic patients and prevented the formation of atherosclerosis in animals and humans (Admin Tradit Chinese Med 1995;5:14; Intl J Orient Med 1990;15:77). We examined the effect of Cs4 in 133 subjects with reduced serum HDL-cholesterol (HDL) on reducing oxidized LDL-cholesterol (oxLDL) and elevating HDL. In this double-blind study, subjects with serum HDL <40 (male) or <45 (female) mg/dL were randomized to a Cs4 (3.0 g/day for 8 weeks) or a placebo (3.0 g/day) group. We found a small reduction of serum LDL in Cs4 group at Week 8 (-5.4%; p=0.002), but no changes in serum total cholesterol, triglycerides, and apoB. HDL was increased by 19.2% with Cs4 (p<0.001); by 31.1% in females and 12.3% in males (p<0.001). Serum apoA1 was increased by 34.7% in Cs4 group (p=0.005). In Cs4 group, serum oxLDL, Atherosclerosis Index, and ratio of oxLDL:HDL were reduced by 22.9% (p=0.001), 29.0% (p<0.001), and 10.5% (p=0.003), respectively. No clinically significant side effects were observed. These findings suggest the health benefits of CordyMax in reducing risk factors of atherosclerosis and ischemic cardiovascular diseases.
ABSTRACT

Objective: To evaluate effects of CordyMax Cs-4, a mycelial fermentation product of Cordyceps sinensis, on energy metabolism.

Design: An in vivo pharmacology study using 31P nuclear magnetic resonance (NMR) spectroscopy.

Subjects and study interventions: Adult male C57-BL/6 mice were given an aqueous extract of CordyMax, 200 or 400 mg/kg per day or placebo for 7 days.

Outcome measurements: Using 31P-NMR spectroscopy to measure cellular triphosphates and inorganic phosphate, expressed as a ratio to a reference peak, and calculate tissue pH.

Results: Steady-state beta adenosine triphosphate (ATP) increased in the liver of mice that received CordyMax (200 or 400 mg/kg per day) for 7 days, by 12.3% +/- 0.8% and 18.4% +/- 0.9%, respectively, compared to placebo controls (both p < 0.001), suggesting a higher hepatic bioenergy status in CordyMax-treated animals. Hepatic inorganic phosphate (Pi) decreased by 24.5% +/- 0.9% and 17.6% +/- 1.7% in the two treatment groups, respectively, compared to placebo controls (p < 0.001). The ratio of beta-ATP:Pi increased by 47.7% +/- 1.6% and 41.4% +/- 2.4%, respectively, in the treatment groups (both p < 0.001 compared to placebo). After discontinuation of CordyMax for 7 days, beta-ATP and Pi returned towards baseline.

Conclusion: CordyMax is effective in improving bioenergy status in the murine liver, suggesting a mechanism underlying the known clinical effectiveness of CordyMax in alleviating fatigue and improving physical endurance, especially in elderly subjects.
The following abstract was presented at the 46th Annual Meeting of the American College of Sports Medicine held in Seattle, WA, June 2-5, 1999. The abstract was published in *Medicine & Science in Sports & Exercise*, the official journal of the American College of Sports Medicine (full citation below). With subscription this same abstract can be viewed at:


When you have accessed the above webpage, scroll to S120, or simply conduct a Ctrl+F search for “Cordyceps Cs-4”.

**Publication Reference:**

**Cordyceps preparation used by Dai et al. in their 1999 publication:** CordyMax™ Cs-4 [Pharmanex (Provo, UT)]

**Enhanced hepatic energy state in mice after administration of a fermentation product of Cordyceps Cs-4.**

**ABSTRACT**

The traditional Chinese herb, *Cordyceps sinensis*, found on the Qinghai-Tibetan plateau, has been advocated for centuries to enhance human vitality. The natural substance has been refined as a mycelial fermentation product of a specific strain of *Cordyceps sinensis* (Cs-4; CordyMax™). Our objective was to study the effect of Cs-4 on tissue energetics using non-invasive $^{31}$P NMR spectroscopy. Studies were performed using male C57-BL/6 mice, weighing 20-22 g, and receiving a standard diet. The animals were divided into three groups. Group A (n=5) received an aqueous extract of fermented Cs-4, 200 mg/kg/day, Group B (n=5) received a higher dose of Cs-4, 400 mg/kg/day, and Group C (n=6) received placebo. All treatments were given by gavage for 7 days and then discontinued. Hepatic $[^{\beta}]\text{-ATP}$ and inorganic phosphate were measured using a $^{31}$P NMR spectroscope (Bruker). The mice were fasted for 6 hours, anesthetized with pentobarbitol (55 mg/kg) by intra-peritoneal injection, and immobilized on shielding belt. An MDPA reference was placed on the back of the coil. Measurements were made at baseline, after 7 days of treatment, and 7 days after discontinuing treatment (washout phase). Tissue pH was calculated from chemical shift differences between [beta]-ATP and Pi. At the end of the treatment phase, [beta]-ATP was increased in relation to the MDPA reference in mice receiving Cs-4 (Group A: 3.81±0.03; Group B: 4.00±0.04; compared with Group C: 3.36±0.04; P<0.001). Inorganic phosphate was decreased in Groups A and B, but not in Group C. Consequently, the ratio [beta]-ATP/PI was also significantly increased in mice receiving Cs-4 (Group A: 4.81±0.05; Group B: 4.50±0.09; compared with Group C: 3.10±0.04; P<0.001). At the end of the washout phase, [beta]-ATP had returned to baseline in Group A and Group B. Hepatic compared with placebo tissue pH was unchanged throughout the study. We conclude that Cs-4 increased hepatic energy state when administered to mice for 7 days. These findings might have broader implications in terms of the reported energizing effect of Cs-4 in human subjects.
ABSTRACT

**Objective:** CordyMax™ Cs-4 (Cs-4) is a standardized mycelial fermentation product of Cordyceps sinensis, a fungus that has been used for various pharmacologic, metabolic, and ergogenic purposes. The goal of this investigation was to determine the effects of oral Cs-4 administration on whole-body insulin sensitivity, skeletal muscle glucose transport, and endurance performance.

**Design:** We studied different indices of carbohydrate metabolism in rats that received Cs-4 orally at a dose of 2 g/kg of body weight daily for 30 days.

**Results:** C-peptide response observed during the oral glucose tolerance test (OGTT) after 10 days of treatment was significantly decreased in the Cs-4-treated group (Cs-4, 52,802 +/- 4,124 vs. control, 70,696 +/- 6309 pM x 120 min; p < 0.05). The integrated insulin area under the curve (53.3 +/- 4.9 ng/mL x 120 minutes) and the glucose-insulin index (6.6 +/- 0.6 units) obtained from the OGTT were significantly decreased (p < 0.01) in the Cs-4-treated group compared to their vehicle-treated counterparts (82.1 +/- 8.1 ng/mL x 120 minutes; 9.9 +/- 0.7 units) after 20 days of treatment. Neither integrated glucose area under the curve observed during either OGTT, basal- or insulin-stimulated 2-deoxyglucose transport nor skeletal muscle GLUT-4 concentrations were affected by Cs-4 treatment. In addition, swim time to exhaustion did not differ between groups in this animal model.

**Conclusion:** We conclude that CordyMax Cs-4 may have potential beneficial effects by maintaining whole-body glucose disposal with a less pronounced increase in insulin secretion after a carbohydrate challenge, however, its effects on endurance performance remain questionable.
CordyMax™ Cs-4 Improves Glucose Metabolism and Increases Insulin Sensitivity in Normal Rats

ABSTRACT

Objective: To evaluate effects of CordyMax trade mark Cs-4, a mycelial fermentation product of *Cordyceps sinensis*, on improving glucose metabolism and insulin sensitivity.

Design: An *in vivo* pharmacology study.

Subjects and Study Interventions: Adult Wistar rats, male and female, were given CordyMax 250 or 500 mg/kg per day or placebo for 17 days by gavage.

Outcome Measurements: Fasting blood glucose, fasting plasma insulin, glucose-insulin index, and oral glucose tolerance.

Results: Rats fed Cs-4 at either 250 or 500 mg/kg showed significantly reduced fasting blood glucose after the 17-day treatment, by 27% and 24% from baselines respectively (both p < 0.001). Examination of fasting plasma insulin demonstrated a 37% decrease in the high dose treatment groups (p = 0.012). Glucose-insulin index, an index of insulin sensitivity, increased by 10% and 17% in both 250 and 500 mg/kg groups (p = 0.008 and p = 0.0001, respectively). Oral glucose tolerance tests showed significantly improved glucose tolerance at 0.5, 1.0, and 2.0 hours after oral administration of a bolus of glucose (the area under the glucose curve: p = 0.05-0.006), but no change at 5 hours.

Conclusion: CordyMax Cs-4 is effective in lowering basal blood glucose and plasma insulin, improving glucose metabolism by enhancing insulin sensitivity, and improving oral glucose tolerance.
The following study was presented at the Experimental Biology (FASEB) meeting in 2010. A full-length study write-up is not available.

Publication reference:

1 Pharmanex Beijing Pharmacology Center, Beijing, China, People’s Republic of
2 Pharmanex Research Institute, Provo, UT
3 School of Pharmacy, Xinjiang Shihezi University, Shihezi, China, People’s Republic of

**Cordyceps preparation used by Tan et al. in their 2010 study:** CordyMax^[C4][Pharmanex (Provo, UT)]

CordyMax extends the lifespan in an aging model: A preliminary report

**ABSTRACT**

Cordyceps sinensis (Cs) is traditionally believed as an anti-aging TCM herb. We have reported the anti-fatigue and endurance enhancement properties of CordyMax (CM), a mycelia fermentation product of Cs, and its benefits in glucose-lipid-energy metabolisms. In this study we examined its anti-aging effects in mice. A total of 192 ICR mice (12 months of age, half males and half females) were randomized into 4 groups, receiving either vehicle or CM at a dose of 0.5, 1.0 or 1.5 g/kg mixed with forage. Calorie intake was monitored twice per week and adjusted carefully to match the calorie intake of controls. Continuous oral CM (72 wks so far) showed: (1) no significant differences in body weight and calorie intake among the groups; (2) compared to controls, the 75% survival time extends 98, 94 and 108 days in the CM groups (0.5, 1.0 and 1.5g/kg, respectively), and the 50% survival time extends 66, 10 and 39 days, respectively. Kaplan-Meier Survivor analysis showed significantly extended lifespan and reduced risks of death by CM: p=0.049 (Wk36), p=0.036 (Wk40), p=0.059 (Wk48), p=0.004 (Wk60), p=0.027 (Wk 64), p=0.041 (Wk 68) with the best survivor curve for the low dose CM treatment (equivalent to the human dose). This study demonstrates that CM extends the lifespan in mice, while the experiment continues. All the health benefits of CM (anti-oxidation, the effect in metabolisms and aerobic exercise capacity) support the anti-aging function of CM.
The following study was presented at the Experimental Biology (FASEB) meeting in 2010. A full-length study write-up is not available.

**Publication reference:**
Yang JY¹, Tan NZ¹, Zhao C¹, Zhang Y¹, Zhu JS²,³. Anti-oxidation activities of CordyMax in an oxidative stress model: A mechanism of its anti-aging property. *FASEB J.* 2010; 24: (Meeting Abstract Supplement) 947.2.

¹ Pharmanex Beijing Pharmacology Center, Beijing, China, People’s Republic of
² Pharmanex Research Institute, Provo, UT
³ School of Pharmacy, Xinjiang Shihezi University, Shihezi, China, People’s Republic of

**Cordyceps preparation used by Yang et al. in their 2010 study:** CordyMax⁴⁻[Pharmanex (Provo, UT)]

Anti-oxidation activities of CordyMax in an oxidative stress model: A mechanism of its anti-aging property

**ABSTRACT**

Cordyceps sinensis (Cs) is traditionally believed as an anti-aging herb. CordyMax (CM), a mycelia fermentation product of Cs, has shown the benefits of lifespan extension, anti-fatigue and improving glucose-lipid-energy metabolisms. We further tested the antioxidant function of CM in mice, the mechanism of its anti-aging effect. Mice were randomized into 5 groups, receiving vehicle or CM at a dose of 0.5, 1.0 or 1.5 g/kg for 60 days by gavage. They were given a single dose of 11 Gry ⁶⁰Co γ-radiation on Day 60 and sacrificed on Day 64. Compared to non-radiation controls, γ-radiation reduced plasma glutathione (GSH) & the thiol groups, liver catalase (CAT) & SOD, GSH-peroxidase (GSH-Px), GSH-reductase (GSH-Rd), and increased liver protein carbonyl groups. Compared to radiation controls, 60 days of oral CM increased plasma thiol groups by 21–25% in the 3 dose groups, and liver CAT by 15–16% (all p<0.01). Oral CM at a dose of 0.5 or 1.0g/kg increased GSH-Px by 15% (p=0.01). CM therapy (1.0 or 1.5g/kg) reduced liver protein carbonyl groups by 9–14% (p=0.04, <0.01) and 8-OHdG by 26–34% (p<0.01); and increased plasma GSH by 26–27% (p=0.02, 0.03), liver GSH-Rd by 10–11% (p=0.02) and liver SOD by 6–9% (p<0.05). In conclusion, oral CM improves antioxidant capacity in mice with radiation-induced oxidative injure, supporting in general the anti-aging activity of CM.
The following study was presented at the Experimental Biology (FASEB) meeting in 2010. A full-length study write-up is not available.

**Publication reference:**
Duan L¹, Zhao L¹, Liang C¹, Lu J², Gao L², Li G¹, Zhu JS³,⁴. Improvement of exercise metabolism and carotenoids antioxidant scores with CordyMax and LifePak in young Chinese elite athletes. *FASEB J.* 2010; 24: (Meeting Abstract Supplement) 805.4.

¹ China national research institute of sports medicine, Beijing, China, People’s Republic of
² Pharmanex Beijing Clinical Center, Beijing, China, People’s Republic of
³ Clinical Pharmacology, Pharmanex Research Institute, Provo, UT
⁴ School of Pharmacy, Xinjiang Shihezi University, Shihezi City, China, People’s Republic of

**Cordyceps preparation used by Duan et al. in their 2010 study:** CordyMaxCs⁴ [Pharmanex (Provo, UT)]

**ABSTRACT**

Cordyceps sinensis and its fermentation product, CordyMax (CM), are used for anti-aging and health preservation. We have reported CM’s anti-fatigue and endurance enhancement functions in multi-sport endurance Caucasians athletes (Chin J Clin Pharmacy 2007, 5:16). LifePak (LP) is enriched in carotenoids and antioxidant nutrients to improve antioxidant capability in young athletes (FASEB J 2009, 23:1007.3). We further tested the improvement of exercise metabolism and antioxidant capacity with CM and LP in a self-controlled trial in young Chinese elite athletes (n=25, 18.1 yrs on average) recruited from China bicycle teams. They received CM 3.18 g/day and LP 2 sachets/day for 6 wks. All subjects remained on the same diet plan and training intensity during the study. Before and after the treatment, subjects performed graded exercise test on cycle ergometer and photonic assays for antioxidant scores. At a work load of 100W, 150W or 200W, RER were reduced significantly by 27%, 31%, & 36% (p<0.001), and blood lactate by 14%, 31% & 33%, and also reduced by 24% & 20% immediately and 3 min after exercise (p<0.05). VO₂ peak, HR and O₂ pulse were not changed in these elite athletes. Carotenoids antioxidant scores were increased by 21% (p=0.02). In conclusion, our data suggest benefits of CM-LP in improving antioxidant capacity and exercise metabolisms to enhance endurance capability and reducing risks of exercise injury in Chinese elite athletes.
The following study was presented at the Experimental Biology (FASEB) meeting in 2011. A full-length study write-up is not available.

**Publication reference:**
Tan NZ¹, Barger JL², Zhang Y¹, Ferguson SB³, Wu ZM¹, Prolla TA², Bartlett M³, Zhu JS¹,³. *Cordyceps sinensis* Cs-4 restores aging-associated changes in gene expression and extends lifespan in normal aged mice. *FASEB J.* 2011; 25:1090.13.

¹ Pharmanex Beijing Pharmacology Center, Beijing, China, People’s Republic of
² LifeGen Technologies, Madison, WI
³ Nu Skin Center for Anti-Aging Research, Provo, UT

**Cordyceps preparation used by Tan et al. in their 2011 study:** CordyMax⁶ Cs-4 [Pharmanex (Provo, UT)]

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**Cordyceps sinensis** Cs-4 restores aging-associated changes in gene expression and extends lifespan in normal aged mice

**ABSTRACT**

*Cordyceps sinensis* is believed to be an anti-aging traditional Chinese herb. We previously reported that *C. sinensis* Cs-4 (a mycelia fermentation product of *C. sinensis*) improves glucose, lipid and energy metabolism and has antioxidant, anti-fatigue and endurance effects. In this study we examined gene expression (GE) profiles of neocortex and gastrocnemius from young (5 months of age), old (25 mo) and old Cs-4 treated (0.3 g/kg) C57Bl/6 mice. Age-related changes in GE were clustered. Cs-4 opposed GE of many changes that occurred with age (p<0.05). This anti-aging effect was examined in a lifespan study in male & female ICR mice fed either control or Cs-4 (0.5, 1.0 or 1.5 g/kg; n=48/group) beginning at 1 year of age. Calorie intake was adjusted twice a week to match the controls. No differences in body weight were noted among the groups. All control mice died before 3 years of age. The lifespan was extended 10–66 days at 50% survival with Cs-4 and 45–153 days at 10% survival. The age of the oldest surviving mice was extended 152 days (1.5 g/kg) and >210 days (both 0.5 and 1.0 g/kg). Kaplan-Meier analysis revealed the best extended lifespan and reduced the risk of death in mice receiving Cs-4 0.5 g/kg (p=0.03). In conclusion, *C. sinensis* Cs-4 reverses age-related changes in GE and extends the lifespan of mice, supporting the traditional belief that *C. sinensis* Cs-4 conveys anti-aging benefits to humans.
The following study was presented at the Experimental Biology (FASEB) meeting in 2011. A full-length study write-up is not available.

**Publication reference:**
Tan NZ\(^1\), Barger JL\(^2\), Zhang Y\(^1\), Ferguson SB\(^3\), Wu ZM\(^1\), Prolla TA\(^2\), Bartlett M\(^4\), Zhu JS\(^1\,3\). The lifespan-extending effect of *Cordyceps sinensis*Cs-4 in normal mice and its molecular mechanisms. *FASEB J.* 2011; 25:599.1.

1 Pharmanex Beijing Pharmacology Center, Beijing, China, People’s Republic of
2 LifeGen Technologies, Madison, WI
3 Nu Skin Center for Anti-Aging Research, Provo, UT

**Cordyceps preparation used by Tan et al. in their 2011 study:** CordyMax\(^{Cs-4}\) [Pharmanex (Provo, UT)]

The lifespan-extending effect of *Cordyceps sinensis*Cs-4 in normal mice and its molecular mechanisms

**ABSTRACT**

*Cordyceps sinensis* is believed to be an anti-aging traditional Chinese herb. We previously reported that *C. sinensis* Cs-4 (a mycelia fermentation product of *C. sinensis*) improves glucose, lipid and energy metabolism and has antioxidant, anti-fatigue and endurance effects. In this study we examined the effects of Cs-4 on lifespan and age-related changes in gene expression (GE) in mice. Male and female ICR mice were fed either control or Cs-4 at 0.5, 1.0 or 1.5 g/kg beginning at 1 year of age (n=48/grp). Calorie intake was adjusted twice a week to match controls. No differences in body weight were noted among the groups. All control mice died before 3 yrs of age while Cs-4 extended lifespan by 10–66 days at 50% survival and 45–153 days at 10% survival. The age of the oldest surviving mice was extended 152 days (1.5 g/kg) and >210 days (both 0.5 and 1.0 g Cs-4/kg BW). Kaplan-Meier analysis revealed the best extended lifespan and reduced risk of death in mice receiving Cs-4 0.5 g/kg (p=0.03). GE profiling of neocortex and gastrocnemius muscle was performed in young (5 mo), old (25 mo) and old Cs-4 treated (0.3 g/kg) C57BL/6J mice. Cs-4 opposed GE of many changes that occurred with age (p<0.05). In conclusion, *C. sinensis* Cs-4 extends the lifespan of mice and reverses many age-related changes in GE, supporting the traditional belief that *C. sinensis* Cs-4 conveys anti-aging benefits to humans.
The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis: part I.

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, antisenescence, endocrine, hypolipidemic, antiatherosclerotic, and sexual function-restorative activities. The safety of the fungus, its effects on the nervous system, glucose metabolism, the 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.
The scientific rediscovery of a precious ancient Chinese herbal regimen: Cordyceps sinensis: part II.

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.
This is an educational publication provided to help licensed healthcare practitioners understand the science upon which CordyMax® Cs-4® is based and the mechanism of action by which CordyMax® Cs-4® works. This pamphlet should not be used to sell CordyMax®.

The only claims that can be made for CordyMax® Cs-4® are those that have been approved by the Company.

A Scientific Product Review

Proprietary Strain of Cordyceps Sinenesis Mycelia
CordyMax®

Reduces Fatigue*

Summary

CordyMax® Cs-4® is a dietary supplement developed and marketed by Pharmanex, LLC to enable people to function at a higher level of activity.*

CordyMax® Cs-4® is an all-natural fermentation product derived from the principle Cordyceps fungal mycelia, Paecilomyces hepiali Chen and fermented on a soy-based liquid nutrient. CordyMax® Cs-4® does not contain additives, preservatives, or added ingredients. Cordyceps’ long history of use in Asia demonstrates an impressive safety record.

What is CordyMax® Cs-4®?

Historical usage of Cordyceps sinensis

Mushrooms were used for food and medicine in China as far back as the Neolithic period, 6,000–7,000 years ago. Today, medicinal mushrooms are growing increasingly popular as foods and as health supplements with special properties. Of all the medicinal mushrooms in China, Cordyceps (Cordyceps sinensis) is unique and the most prized. Cordyceps is officially recognized in China as a national medicinal treasure, a precious, practically sacred, tonic-food that has been used as a powerful restorative for at least the last 1,000 years. Cordyceps received world-wide attention when American news magazines interviewed China’s record-breaking athletes who revealed to reporters that they took the mushroom as a post-exercise recovery food between events. Since then, research on Cordyceps has greatly increased in China. So far, over 2,000 people have been tested with the mushroom in clinical studies to uncover the secret of its health benefits.

Cordyceps sinensis (Berk.) Sacc. (Cordyceps) is also known as Chinese caterpillar fungus or summer grass, winter worm (Dong Chong Xia Cao in Chinese, or Chong Cao for short). For thousands of years, the only descriptions of Cordyceps were those of the ancient Chinese who alluded to the existence of a strange organism with the amazing ability to transfigure itself into a plant and then back again into an animal. Details of using Cordyceps medicinally first appeared during the Ching Dynasty in the books Newly Revised Materia Medica (Ben Cao Chong Xin, 1757 A.D.) and Supplement to Ben Cao Gang Mu (Ben Cao Gang Mu Shi Yi, 1765 A.D.) by Chao Xue-Ming.

In China, Cordyceps sinensis is a Traditional Chinese Medicine (TCM) herb of choice to support lung and kidney health. The ancient records claimed that Cordyceps is beneficial to the heart, circulatory system, liver, kidneys, respiratory system, sex organs, and immune system.*

Due to the scarcity and limited supply of wild Cordyceps, its use in ancient times was reserved almost exclusively for the Emperor’s palace.

Nature of Cordyceps sinensis

Cordyceps is a rare, capless type mushroom found at altitudes of 9,000 to 16,000 feet in the high mountain grasslands of Tibet and Southwestern China. It belongs to a diverse group of fungi that includes the truffles and morels. Its Latin name, Cordyceps sinensis (Berk.) Sacc., describes the swollen head (Cordyceps) appearing at the top of the mushroom, which is only slightly larger than the stalk, and a dark brown to black body resembling a small blade of grass or an upright twig. The name sinensis simply means Chinese.

Cordyceps has two distinct components: a parasitic mushroom and a caterpillar host. The mushroom, Cordyceps sinensis (Berk.) Sacc., is a rare parasitic mushroom that grows on and extracts nutrients from a certain species of caterpillar, which, in this case, is primarily Hepialus armoricana Oberthür. It takes five to seven years for Cordyceps to complete its life cycle, mainly because only 4- to 6-year-old Hepialus caterpillars are vulnerable to infection by the mushroom (Dinghua 1995).

At maturity, Cordyceps’ ascus spreads its spores on the ground, and the spores are carried underground by rain water. Hepialus caterpillars reside six inches underground and feed on roots of Polygonum viveparum L. In late autumn, certain unknown chemicals on the skin of mature (4 to 6 years old) caterpillars interact with the fungal spores and release their fungal mycelia, which infects and proliferates inside the caterpillar body. By early summer of the following year, the caterpillar dies from mycelia infestation and a two-inch fungal fruit body from the tail of the caterpillar appears. The final stage of this specimen is called Cordyceps sinensis. The principle fungal mycelia of Cordyceps sinensis is Paecilomyces hepiali Chen (Cs-4®).
Recent scientific advances have literally brought the mushroom down from the mountains. Using cell culture technology, researchers have found a way to grow Cordyceps commercially. The cultured mycelium (underground section) of the mushroom is just as effective or more so than the rare and expensive wild one (Chen 1992). Using a high-tech process, the mycelium can be grown in much the same way as yeast used in baking and brewing. Provided just the right nutrients, environment, and other conditions, the mycelium of Cordyceps holds virtually the same biological activity of the wild form.

The research on cordyceps in China has been extensive, with the result that today there are a number of mycelial products. Each has a different name and special conditions for successful growth in culture. The most developed and extensively studied strain is Cs-4® (Paecilomyces hepiali), which is grown using a basic medium made of soybean.

**Mechanism of Action**

CordyMax® Cs-4® and wild cordyceps have been found to contain seven basic natural product classes: 3–7 (1) proteins, peptides, amino acids, and polyamines; (2) saccharides and sugar derivatives; (3) sterols; (4) nucleosides; (5) fatty acids and other organic acids; (6) vitamins; and (7) inorganic elements.

CordyMax® Cs-4® and wild cordyceps also contain all the essential amino acids for humans (Fei 1992, Yue 1995). In addition, a class of unique cyclic di-peptides are present, such as:

- cyclo- (Gly-Pro), cyclo- (Leu-Pro), cyclo- (Val-Pro), cyclo- (Ala-Leu), cyclo- (Ala-Val), and cyclo- (Thr-Leu).

Cyclo- (Gly-Pro) may have pharmacological effects on immune function.*

Saccharides (polysaccharides and oligosaccharides) and sugar derivatives (e.g., D-mannitol) were identified and their pharmacological activity has been reported (Yue 1995).

D-mannitol (originally identified as cordycepic acid) has been selected as one of the marker molecules for standardizing cordyceps preparations. A group of interesting oligo- and polysaccharides (Cs-1) isolated from natural cordyceps stimulates macrophage function, and promotes lymphocyte transformation.*

A bioactive 23-kD protein bound polysaccharide was shown to consist mainly of mannose and galactose in a ratio of three to five, together with protein.

Sterols isolated from both CordyMax® Cs-4® and wild cordyceps include ergosterol, Δ7-ergosterol, ergosterol peroxide, β-sitosterol, daucosterol, and campesterol.

Eleven nucleosides compounds have been found in CordyMax® Cs-4® and wild cordyceps. Major nucleosides in Cs-4® are adenosine (one of the bioactive marker molecules for standardization), adenosine, uracil, uridine, guanosine, thymidine and deoxyuridine.

Twenty-eight saturated and unsaturated fatty acids and their derivatives have been isolated (Huang 1991, Yue 1995). Polar compounds of crdyceps extracts and Cs-4® include compounds of hydrocarbons, alcohols, and aldehydes (Fei 1992, Zhu 1998).

**Product Benefits**

**Fatigue-Fighting Function**

Numerous scientific studies suggest that CordyMax® Cs-4® may promote natural vitality and reduce fatigue.*

Fatigue has been defined as the self-recognized state in which an individual experiences a sustained sense of exhaustion and decreased capacity for physical and mental work (Carpenito 1995).

Cordyceps has been shown to:

- Reduce oxidative stress by scavenging oxygen free radicals in mitochondria.*
- Promote efficient utilization of oxygen.*
- Elevate energy states (ATP) in organs.*
- Redistribute blood flow to essential organs.*
- Improve liver and kidney functions through metabolizing and excreting toxic substances.*
- Provide a positive benefit for sexual health.*

**Energy, Vitality, and Endurance Enhancement**

Energy, Vitality, and Endurance Enhancement Cordyceps has been known for centuries for its benefits as a tonic against aging.* Recently, several papers reported clinical improvement of vitality, coupled with an increase in superoxide dismutase (SOD) activity and a decrease in oxygen free radicals (Zhang 1995, Cao 1993). It is generally recognized that one of the factors related to aging is a dramatic reduction of cellular superoxide dismutase (SOD) functions, leading to an accumulation of excessive oxygen free radicals and oxidative damage to cells.

In an animal study reported at the 46th annual meeting of the American College of Sports Medicine, CordyMax® Cs-4® was shown to enhance the hepatic energy state in mice (Dai 1999). Research performed in China indicated that CordyMax® Cs-4® (5 g/kg, intraperitoneally, or 10 g/kg, orally) dramatically reduced oxygen consumption of mice (Lou 1986).

The mice lived longer, with an average survival time of 67 and 49 minutes after intraperitoneal or oral CordyMax® Cs-4® respectively. CordyMax® Cs-4®

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induced reduction of oxygen consumption and prolonged survival in a hypoxic environment may suggest enhanced adaptation to a low oxygen environment.*

In a separate study (Bao 1988), CordyMax® Cs-4® (5–20 g/kg) significantly prolonged survival of mice in a dose dependent fashion. Notably, natural cordyceps treatment significantly increased the ability of Yang asthenia mice to endure cold, as measured by the survival of mice in freezing temperature (Bao 1988).

The level of 86RbCl (an index of metabolic activity and increased blood flow) increased in the heart and brain of mice given subcutaneous injection of Cs-4® (10 to 20 g/kg) (Zhang 1990). Blood flows increased by 114 percent in heart and 45.7 percent in brain in mice treated with the higher dose of Cs-4®.

A study presented at the 46th annual meeting of the American College of Sports Medicine showed that CordyMax® Cs-4® can increase aerobic capacity in healthy elderly humans (Xiao 1999). In a double-blind, placebo-controlled trial, the CordyMax® Cs-4® effects were tested on 30 healthy, elderly subjects randomly assigned to receive three grams a day of either CordyMax® Cs-4® or placebo. Exercise performance was tested before and after six weeks of treatment using a symptom-limited, incremental work rate protocol on a cycle ergometer. Those subjects taking CordyMax® Cs-4® during the six-week trial significantly increased maximum oxygen uptake from 1.88 to 2.00 liters per minute. Those taking the placebo exhibited no change in performance.*

In one clinical study, 66 elderly participants on CordyMax® Cs-4® (3 g/day for three months), 18 had a significant (15%) increase in SOD activity and better vitality and energy scores, including a higher tolerance to cold than the control group (Zhang 1995).

Several animal studies have also shown the benefits of CordyMax® Cs-4®.

Together these studies indicate that CordyMax® Cs-4® and cordyceps may be promoting more efficient usage of oxygen under stress conditions and increase tissue steady-state energy levels.* The biochemical mechanism of these effects, however, is not well understood. Besides enhanced vascular flow to essential organs, another hypothesis is related to protection of intracellular mitochondria, the cellular energy machinery, from oxygen free radicals.* CordyMax® Cs-4® and cordyceps may modulate immune function (Zhang 1990, Chen 1985, Liu 1985, Wang, 1987) and optimize endocrine systems (Fei 1992, Zhu 1998, Wang 1987, Wan 1988).*

The improvement in endocrine and immune functions could influence better physical strength.

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**Promotes Healthy Lung Function**

In TCM, cordyceps is said to keep the lungs fit, and is called lung-nourishing.* Cordyceps helps keep the lungs healthy through its ability to increase the activity of the body's own antioxidant, SOD.* The lung is bombarded with free radicals (pollution, dust, smoke) and can only defend itself by producing endogenous antioxidant free radical scavengers, such as SOD.

In animal studies (Zhu 1998) CordyMax® Cs-4® (6 g/kg, intragastric infusion) increased intratracheal secretion. The increase in secretion reached a peak during the second hour after taking CordyMax® Cs-4®.

In a clinical study participants were placed on a course of cordyceps mycelium powder (three 330 mg capsules, three times a day) for 21 days showed a highly significant increase (35.7%) in levels of the naturally occurring antioxidant SOD compared to their pre-cordyceps reading. The increase indicated to the investigators that tissue repair and protective mechanisms had gone into higher gear.*

**Heart Health**

One of the longest clinical studies ever conducted with CordyMax® Cs-4® was completed in 1995. Researchers at Fu-Jian Medical College in China set out to test Cs-4® for its potential effects on the quality of life of 64 study participants. The participants were randomly assigned to one of two groups.

The dosage of the Cs-4® used was 3–4 g/day in capsules for an average of 26 months. The participants were regularly checked for changes in their ECGs, quality of life, and other measurements.*

The investigators found very significant differences in all measurements including shortness of breath/fatigue index, the control group alone improved by an average of 25 percent. But in the group receiving Cs-4®, the improvement averaged 66 percent. Ultrasound revealed that a considerable improvement had occurred in the Cs-4® group, whereas the improvement in the control group was only modest.

Statistically significant improvements showed up in the Cs-4® group in their cardiac output, stroke volume, and heart beat.*

Measurable improvements were found in general activities in 12 of the 30 control study participants, whereas among those on cordyceps group, 27 out of 34 had improved. Improvements in general well-being and in psychological status were also statistically greater in the Cs-4® group compared to the controls. In terms of psychological status, the improvement in the Cs-4®

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group was 25 percent greater than the control group, and in general well-being the Cs-4® group index reached 5.6 versus 4.1 for the controls. A significantly greater number in the Cs-4® group experienced an increase in feeling comfortable and an increase in self-control.*

**Cordyceps and Healthy Cholesterol Levels**

A recent double-blind study was presented at the American Heart Association's (AHA) Scientific Sessions. Subjects with reduced serum HDL-c were given CordyMax® Cs-4® or placebo (3.0 g/day) for eight weeks to study the effects of reducing oxidized LDL-c and elevating HDL. There was a small benefit to serum LDL in the Cs-4® group and HDL had increased 19.2% compared to placebo. Finding from this study provide substantiation for the cardiovascular benefits of CordyMax® Cs-4®.

The largest study of cordyceps in China for maintaining normal existing cholesterol levels was a multicenter clinical trial at nine hospitals with 273 patients. Cordyceps was shown to promote healthy HDL-c levels, which increases the number of LDL-c that gets carried away for elimination.

In two placebo-controlled clinical trials in elderly participants, Cs-4® was shown to reduce the age-related oxidation of fats in the system. The red blood cells of 60 to 84-year-old study participants on Cs-4® (3 g/day for three months) had significantly higher levels of one of the body's own antioxidants, and enzyme called superoxide dismutase (SOD). SOD levels increased so much after the participants took Cs-4® (from 882.74 ± 138.05 to 1021.16 ± 144.95) that they reached levels comparable to those of 17- to 20-year-olds (949.16 ± 125.18) who were checked for comparison.*

A study of individuals on Cs-4® for four weeks also showed a significant decrease in cell-damaging free radicals known as lipoperoxides. Lipoperoxides are formed when lipids (fats) in the body are oxidized or burnt by the system. Researchers can measure them in the form of something called plasma malondialdehyde, or MDA levels. The MDA levels were initially higher in the elderly participants, but after 23 months on Cs-4® levels became significantly lower, so low they reached levels found in the 17- to 20-year-olds. These findings indicate that cordyceps (Cs-4®) reduces oxidative damage to cells caused by free radicals which is important to maintaining healthy artery walls.*

**Proprietary Processing**

Beginning in 1972, researchers at the prestigious Institute of Materia Medica of the Chinese Academy of Medicinal Sciences labored for 10 years collecting and analyzing cordyceps from every corner of China. Because cordyceps is both rare and very difficult to collect, their goal was to develop a superior strain of the mushroom for mycelial production to supply an increasing demand. Cs-4® the cordyceps strain they finally arrived upon, was selected from 200 others. In order to be selected, it had to meet rigorous standards of safety, be able to grow in a variety of media, grow rapidly, and have little chance of becoming contaminated. Cs-4® was found at an altitude of over 12,400 feet in Huolong in the Province of Qinghai, an area traditionally renown for the mushroom for millennia. In 1987, China's Ministry of Public Health approved Cs-4® for use by the general public. Later, it won national awards and became the first traditional Chinese medicine officially approved in the country since traditional medicines began evaluation under China's new, more stringent Western scientific methods for approval.

The fermentation product, CordyMax® Cs-4® also known as Jin Shui Bao in Chinese, has been profiled extensively by chemical and pharmacological methods. Cs-4® appears to come closest to the wild mushroom in the way that the stage of fermentation uses cold temperatures, the similarity of its outward appearance when allowed to grow to maturity, the similarity of its chemical components, and in its beneficial actions as a herbal supplement. Studies have shown that Cs-4® has, in some instances, proven more effective than the wild form (Chen 1992).

In 1995, Cs-4® was placed under intellectual property protection by the Chinese government.

**Side Effects**

With the exception of one case of allergic skin reaction, no other severe adverse effects have been reported from clinicians and hospital records in China since the initial introduction in 1989.

Clinical trials revealed very few side effects to supplementation with CordyMax® Cs-4®. Some subjects noted a sensation of thirst which decreased with continued use, one subject reported slight nausea, and several subjects noted heartburn if CordyMax® Cs-4® was taken before meals; all these effects were well-tolerated by the subjects, and none of these subjects discontinued supplementation because of these effects.

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Safety and Toxicology Data

CordyMax® Cs-4® is well-tolerated (Fei 1992, Guo 1986, Zhu 1998). Acute toxicity studies could not define an oral LD 50 in mice. No incidence of toxic reaction has been reported. Acute toxicity studies, oral administration to mice showed no death at 80 g/kg body weight, which is over 1,000 times the recommended human daily dose. A three-month sub-chronic toxicity study was conducted in rats fed with CordyMax® Cs-4® at a dose of 1, 2, or 3 g/kg/day, equivalent to 20, 40, or 60 times of the human dose, respectively (Zhu 1998). Rats in the treatment group showed similar growth (increase in body weight) with normal CBCs, liver, and renal functions when compared to placebo control. No morphological changes were observed in organs of CordyMax® Cs-4® treated rats.

Mice treated with CordyMax® Cs-4® at oral doses of 3, 5, or 10 g/kg (60, 100, or 200 times the human dose) for 30 days did not exhibit any significant abnormal effects. Microscopic examination after 30 days of treatment did not reveal any abnormalities in the organs, except for slightly opaque-swollen kidneys in only a few mice treated with the highest dose group (200 times of the human dose). Dogs treated for three months with CordyMax® Cs-4® at a dose approximately equal to three times the human dose showed no adverse effects on body and organ weight, growth, hematology, or clinical chemistry (Guo 1986, Zhu 1998). CordyMax® Cs-4® is non-mutagenic and non-teratogenic (Guo 1986, Zhu 1998).

Drug Interaction

No information is available on drug interactions with Cordyceps sinensis; however, due to the content of adenosine in the fungus, the inhibition of platelet aggregation may affect patients on blood-thinning and antithrombotic medication (Shiao 1994).

Cultured cordyceps mycelium extracts have been reported to display significant inhibition of monoamine oxidase type B in in vitro assays (Xu 1988). There is, however, no published data on the effect of these extracts on MAO-B in vivo. Patients receiving MAO inhibitors are advised to consult with a physician before using CordyMax® Cs-4®.

Directions for Use

As a dietary supplement for adults, take two capsules two or three times daily with food and drink. CordyMax® Cs-4® should be taken regularly for consistent results. Mild effects may be evident within one week, while significant effects may take three to six weeks to become evident.

How Supplied

CordyMax® Cs-4® capsules (525 mg each) are supplied in a one-month supply of 120 capsules. The dark brown powder is enclosed in easy-to-swallow clear gelatin capsules. Clear gelatin capsules are USP quality and are designed to disintegrate within 30 minutes after ingestion.

Storage

Store in dry, cool place. Avoid excessive heat. Protect from light.

Shelf Life

Expiration date and lot code numbers are imprinted on the bottom of the box.

Warnings

CordyMax® Cs-4® has not been evaluated in children and should only be used by adults. Because there are no adequate and well-controlled studies in pregnant or lactating women, this product should not be used during pregnancy or lactation without the advice of a physician.
References

5. Dai GW, Bao TT, Xu CF, Cooper R, Zhu JS, Cooper CB. Enhanced hepatic energy state in mice after administration of a fermentation product of Cordyceps Cs-4® Medicine & Science in Sports & Exercise 1999(supp);31(5):S120.
The Pharmanex® 6S Quality Process

The Pharmanex® 6S Quality Process is central to the Pharmanex® mission of transforming time-honored, traditional preparations into health promoting botanical products with known content and consistent activity.

| Selection | • Exhaustive scientific review of research and databases is conducted.  
|           | • Authenticity, usefulness, and safety standards are determined. |
| Sourcing  | • Teams of experts investigate potential sources and evaluate quality.  
|           | • Comprehensive botanical and chemical evaluations are completed. |
| Structure | • Structural analyses of natural compounds are determined.  
|           | • Active ingredients are isolated and studied. |
| Standardization | • Strict standardization to at least one relevant marker molecule is required.  
|             | • Proprietary processing methods to increase consistency and ensure measured dose effectiveness are developed. |
| Safety    | • Safety is assessed from available research.  
|           | • Microbial test, chemical, toxin, and heavy metal analyses are conducted. |
| Substantiation | • Documented pre-clinical and clinical studies are reviewed.  
|             | • Pharmanex sponsored studies are initiated when appropriate. |

For More Information:
To learn more about the Pharmanex® line of natural healthcare products, please call Customer Service 1-800-487-1000 or FAX us at 1-800-800-0259.

Visit our Web site and access information directly at www.pharmanex.com