

CordyMax Studies Compendium

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Tan NZ, Zhang Y, Yang JY, Zhao C, Zhu JS. CordyMax extends the lifespan in an aging model: A preliminary report. <i>FASEB J.</i> 2010; 24: (Meeting Abstract Supplement) 947.1.15
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Tan NZ, Barger JL, Zhang Y, Ferguson SB, Wu ZM, Prolla TA, Bartlett M, Zhu JS. <i>Cordyceps sinensis</i> Cs-4 restores aging-associated changes in gene expression and extends lifespan in normal aged mice. <i>FASEB J.</i> 2011; 25:1090.13.18
Tan NZ, Barger JL, Zhang Y, Ferguson SB, Wu ZM, Prolla TA, Bartlett M, Zhu JS. The lifespan-extending effect of <i>Cordyceps sinensis</i> Cs-4 in normal mice and its molecular mechanisms. <i>FASEB J.</i> 2011; 25:599.1.19

REVIEW ARTICLES AUTHORED BY PHARMANEX SCIENTISTS

Zhu JS, Halpern GM, Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: <i>Cordyceps sinensis</i> . Part I. <i>J Altern.Complement Med.</i> 1998; 4(3): 289-303.20
Zhu JS, Halpern GM, Jones K. The scientific rediscovery of a precious ancient Chinese herbal regimen: <i>Cordyceps sinensis</i> . Part II. <i>J Altern.Complement Med</i> 1998;4: 429-57.21

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: <http://journals.lww.com/acsm-msse/pages/toc.aspx?year=2001&issue=05001>

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

Publication Reference:

Nicodemus KJ¹, Hagan RD¹, Zhu J², Baker C¹. Supplementation with Cordyceps Cs-4 fermentation product promotes fat metabolism during prolonged exercise. *Medicine and Science in Sports and Exercise* 2001; 33(5) Supplement 1:pg S164 (Abstract# 928).

¹Fit Stop Human Performance Laboratory, Encinitas, CA.

²Pharmanex 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_{2peak}) 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 ($4.5 \text{ gm} \cdot \text{day}^{-1}$) 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_{2peak} of $62.6 \pm 7.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) 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_{2peak}). 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 15th 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 30th 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.

Publication reference:

Zhu JS¹, Nicodemus KJ², Hagan RD², Baker C². CordyMax Cs-4 improves cardiovascular and metabolic capacity during exercise in highly-fit athletes. *FASEB Journal* 16(4): A628; 2002.

¹Pharmanex, 75 West Center St., Provo, UT 84601

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

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:

Zhu JS, Yin WT, Nicodemus KJ, Zhao CS, Baker, C, Wang JY. CordyMax Cs-4 improves glucose metabolism. *FASEB Journal Meeting Abstracts*, 2001; 15: Abstract# 753.

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 O₂ 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; VO₂peak 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% VO₂peak, 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: <http://journals.lww.com/acsm-msse/pages/toc.aspx?year=1999&issue=05001>

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

Publication Reference:

Xiao Y, Huang XZ, Chen G, Wang MB, Zhu JS, Cooper CB, FACSM, Increased aerobic capacity in healthy elderly humans given a fermentation product of Cordyceps Cs-4. *Medicine and Science in Sports and Exercise* 1999; 31(5) Supplement: pg S174 (Abstract# 774).

Cordyceps preparation used by Xiao *et al.* in their 1999 publication: CordyMax^{Cs-4} [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 (VO₂max) was measured using a metabolic cart. Anaerobic thresholds (VO₂θ) were identified by two observers using plots of both VCO₂ versus VO₂ and V_{EQ}O₂ versus time. The results were as follows:

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

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

After taking Cs-4 for 6 weeks, VO₂max and VO₂θ 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.

The following abstract was presented at the *Nutrition Week* Meeting in San Diego, California, February 23-27, 2002. This same abstract was published in journals: the *American Journal of Clinical Nutrition*, a publication of the **American Society for Nutrition** (full citation below). **This same abstract was presented at the American College of Sports Medicine (Southwest Chapter) annual meeting** in Salt Lake City, UT, November 16-17, 2001.

<http://www.ajcn.org/cgi/reprint/75/2/339S.pdf>

When you have accessed the above webpage, scroll to page 401S.

Publication reference:

Talbott SM¹, Zhu JS¹, Rippe JM². Cordymax Cs-4 Enhances Endurance in Sedentary Individuals. *Am J Clin Nutr*, 75:2(Suppl), 2002, pg 401S, Abstract# P200.

¹Pharmanex, LLC, Provo, UT; ²Rippe Lifestyle Institute, Shrewsbury, MA

Cordyceps preparation used by Talbott *et al.* in their 2002 publication: CordyMax^{Cs-4} [Pharmanex (Provo, UT)]

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 (VO₂max) 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 VO₂peak, respiratory exchange ratio (RER), 1-mile walk time, and work output (Jeukendrup bike test), were performed at baseline and 12 weeks. VO₂peak increased 5.5% in Cs-4 (p = 0.003) but only 2.1% in P (NS). Exercise time to VO₂peak 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)]

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:

Chen S, Li Z, Krochmal R, Abrazado M, Kim W, Cooper CB. Effect of Cs-4 (Cordyceps sinensis) on exercise performance in healthy older subjects: a double-blind, placebo-controlled trial. J Altern Complement Med. 2010 May;16(5):585-90.

Cordyceps preparation used by *Chen et al.* in their 2010 publication: CordyMax^{Cs-4} [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(+) 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 $\dot{V}O_2$ 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:

Zhu JS, Pei Y, Wang B, Rippe J. CordyMax reduces serum oxidized LDL-cholesterol and increases HDL-cholesterol in humans with reduced HDL-cholesterol. *Circulation Suppl IV*;108(17), 2003:Abstract# 3524.

Cordyceps preparation used by *Zhu et al.* in their 2003 publication: CordyMax^{Cs-4} [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.

Copyright laws prohibit the distribution of un-paid for copies of the full-length *Dai 2001* article; however, for your convenience please find the study abstract below. This same abstract is available at the following internet link:

<http://www.ncbi.nlm.nih.gov/pubmed/11439844>

Publication reference:

Dai G, Bao T, Xu C, Cooper R, Zhu JS. CordyMax Cs-4 improves steady-state bioenergy status in mouse liver. *J Altern Complement Med.* 2001 Jun;7(3):231-40.

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

CordyMax Cs-4 improves steady-state bioenergy
status in mouse liver.

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: <http://journals.lww.com/acsm-msse/pages/toc.aspx?year=1999&issue=05001>

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

Publication Reference:

Dai GW, Bao TT, Xu CF, Cooper R, Zhu JS, and Cooper CB., Enhanced hepatic energy state in mice after administration of a fermentation product of Cordyceps Cs-4. *Medicine and Science in Sports and Exercise* 1999; **31**:S120 (Abstract# 464).

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 ³¹P 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]-ATP and inorganic phosphate were measured using a ³¹P 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.

Copyright laws prohibit the distribution of un-paid for copies of the full-length *Balon 2002* article; however for your convenience please find the study abstract below. This same abstract is available at the following internet link:

<http://www.ncbi.nlm.nih.gov/pubmed/12165189>

Publication reference:

Balon TW, Jasman AP, Zhu JS. A fermentation product of *Cordyceps sinensis* increases whole-body insulin sensitivity in rats. *J Altern Complement Med.* 2002 Jun;8(3):315-23.

Cordyceps preparation used by Balon *et al.* in their 2002 publication: CordyMax^{Cs-4} [Pharmanex (Provo, UT)]

A fermentation product of *Cordyceps sinensis* increases whole-body insulin sensitivity in rats.

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.

Copyright laws prohibit the distribution of un-paid for copies of the full-length *Dai 2002* article; however, for your convenience please find the study abstract below. This same abstract is available at the following internet link:

<http://www.ncbi.nlm.nih.gov/pubmed/12165188>

Publication reference:

Zhao CS, Yin WT, Wang JY, Zhang Y, Yu H, Cooper R, Smidt C, Zhu JS. CordyMax™ Cs-4 improves glucose metabolism and increases insulin sensitivity in normal rats. *J Altern Complement Med.* 2002 Jun;8(3):309-14.

Cordyceps preparation used by Zhao *et al.* in their 2002 publication: CordyMax^{Cs-4} [Pharmanex (Provo, UT)]

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:

Tan NZ¹, Zhang Y¹, Yang JY¹, Zhao C¹, Zhu JS^{2,3}. CordyMax extends the lifespan in an aging model: A preliminary report. *FASEB J.* 2010; 24: (Meeting Abstract Supplement) 947.1.

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Cordyceps preparation used by Tan *et al.* in their 2010 study: CordyMax^{Cs-4} [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 JS^{2,3}. 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.

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Cordyceps preparation used by Yang *et al.* in their 2010 study: CordyMax^{Cs-4} [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 injury, 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 JS^{3,4}. 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.

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Cordyceps preparation used by Duan *et al.* in their 2010 study: CordyMax^{Cs-4} [Pharmanex (Provo, UT)]

Improvement of exercise metabolism and carotenoids antioxidant scores with CordyMax and LifePak in young Chinese elite athletes

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 JS^{1,3}. *Cordyceps sinensis* Cs-4 restores aging-associated changes in gene expression and extends lifespan in normal aged mice. *FASEB J.* 2011; 25:1090.13.

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

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 NZ¹, Barger JL², Zhang Y¹, Ferguson SB³, Wu ZM¹, Prolla TA², Bartlett M³, 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.

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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.

Copyright laws prohibit the distribution of un-paid for copies of the full-length *Zhu 1998* article; however, for your convenience please find the study abstract below. This same abstract is available at the following internet link:

<http://www.ncbi.nlm.nih.gov/pubmed/9764768>

Publication reference:

Zhu JS, Halpern GM, Jones K., The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis*: part I. *J Altern Complement Med.* 1998 Fall;4(3):289-303.

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.

Copyright laws prohibit the distribution of un-paid for copies of the full-length *Zhu 1998* article; however, for your convenience please find the study abstract below. This same abstract is available at the following internet link:

<http://www.ncbi.nlm.nih.gov/pubmed/9884180>

Publication reference:

Zhu JS, Halpern GM, Jones K., The scientific rediscovery of an ancient Chinese herbal medicine: The scientific rediscovery of a precious ancient Chinese herbal regimen: Cordyceps sinensis: part II. *J Altern Complement Med.* 1998 Winter;4(4):429-57.

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.