Lipid-lowering effect of cordycepin (3'-deoxyadenosine) from *Cordyceps militaris* on hyperlipidemic hamsters and rats

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Abstract: 3'-Deoxyadenosine, so-called cordycepin, is a bioactive component of the fungus *Cordyceps militaris*. It has been known to exhibit multiple-biological effects including: modulation of immune response, inhibition of tumor growth, hypotensive and vasorelaxation activities, and promoting secretion of adrenal hormone. To investigate its lipid-lowering effect, hyperlipidemic hamsters and rats fed by high-fat diet were both administered orally with cordycepin extracted from *Cordyceps militaris* for four weeks. The levels of lipids in hamsters and rats were measured enzymatically before and after the administration of cordycepin (12.5, 25 and 50 mg·kg^{-1}). The results suggested that levels of serum total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) increased markedly in the two animal models by feeding high-fat diet. Meanwhile, cordycepin reduced levels of serum TC, TG, LDL-C, VLDL-C as well as LDL-C/HDL-C (high density lipoprotein cholesterol) and TC/HDL-C ratios. In concert with these effects, an increase in lipoprotein lipase (LPL) and hepatic lipase (HL) activity afforded by cordycepin was considered to contribute to the regulation on lipid profiles. Furthermore, no toxicity of cordycepin was observed by intragastric administration at the maximal tolerant dose in ICR mice for 14 days. The exact lipid-lowering effect of cordycepin needs further investigation.

Key words: *Cordyceps militaris*; cordycepin; lipid-lowering effect; hyperlipidemia

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蛹虫草提取物虫草素 (3'-脱氧腺苷) 对于高脂血症地鼠和大鼠的降血脂作用研究

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摘要: 3'-脱氧腺苷 (又名虫草素) 是从蛹虫草子实体中分离得到的一个具有生物活性的化合物。研究发现，虫草素具有多种生物效应，包括: 调节免疫应答，抑制肿瘤生长，降压和舒张血管，促进肾上腺激素的分泌等。为研究其降血脂作用，本研究选用高脂饲料诱导的高脂血症金黄地鼠和大鼠，每天灌胃给予虫草素 (12.5，25 和 50 mg·kg^{-1}) 共 4 周。在给药前及给药 4 周后，通过酶学方法测定地鼠和大鼠的血脂水平。结果显示，在饲喂高脂饲料后，两种动物的血清中总胆固醇 (TC)，甘油三酯 (TG)，低密度脂蛋白胆固醇 (LDL-C) 和极低密度脂蛋白胆固醇 (VLDL-C) 水平显著上升。同时，虫草素均可降低这两种动物血清中 TC、TG、LDL-C、VLDL-C (高

密度脂蛋白胆固醇) 含量及 LDL-C/HDL-C 和 TC/HDL-C 的比值, 认为虫草素组动物脂蛋白酯酶 (LPL) 和肝酯酶 (HL) 活性的上升与调控血脂水平有关。另外, 对 ICR 小鼠按照最大耐受剂量灌胃给予虫草素 (5 g·kg^{-1}) 14 d 后, 并没有出现明显的毒性反应。虫草素降血脂的作用机制仍需进一步研究。

关键词: 蛹虫草; 虫草素; 降血脂作用; 高脂血症

Dyslipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions, such as coronary heart disease (CHD), ischemic cerebrovascular disease and peripheral vascular disease, which still account for the majority of morbidity and mortality among middle-aged and elder adults[1]. Recognition of hyperlipidemia as a risk factor has led to the development of drugs that reduce cholesterol and triglycerides levels or both. These drugs include statins, HMG-CoA reductase inhibitors, bile acid binding resins, nicotinic acid, fibric acid derivatives and so on. However, more and more postmarketing surveillance studies of these drugs have proven that the adverse effect revealed up, including hepatotoxicity[2], myopathy[3], flushing[4], dyspepsia[5], etc. Therefore, the discovery and development for novel hypolipidemic drugs are urgently required. The seek for new drugs of HMG-CoA reductase inhibitors or fibric acid derivatives capable of reducing and/or regulating lipid profile with minimize side effects, has gained momentum over the years, resulting in numerous reports on significant activities of natural agents[6−8].

Accumulative information has shown that it might be a good way to find the leading compounds, even candidates, from natural products, which their chemical structures might be different from those well-known marketing hypolipidemic drugs. Cordyceps sinersis, known as "Dong Chong Xia Cao" (summer-plant, winter-worm), has been commonly used in traditional Chinese medicine for the treatment of dyslipidemia for centuries[9]. Unfortunately, wild Cordyceps sinersis is rare and it is very difficult to culture artificially. On the other hand, Cordyceps militaris is another genus of cordyceps, which is widely used in China and many countries in Southeast Asia nowadays. Although this fungus has been utilized in Chinese herbal medicinal prescriptions for the relief of hyperlipidemia for a long time, there is a relative scarcity of definite evidence to establish its hypolipidemic pharmacological acitivity.

In the present study, we investigated the lipid-lowering effect of cordycepin (3'-deoxyadenosine), extracted from Cordyceps militaris on the hyperlipidemic hamsters and rats; in addition, we tested the activities of enzymes, LPL and HL, which have much to do with lipid metabolism. Besides, in order to show its biological safety, an acute toxicity test on ICR mice was conducted.

Materials and methods

Extraction and purification of cordycepin   One kilogram of the cultured fruiting body *Cordyceps militaris* (L.) Link (provided by Hunan Yikang High-tech Biology Co., Ltd.) was soaked in EtOH over night, and extracted by thermal recycling extraction for 3−4 h (totally extracting for 3 times). The extract solution was concentrated under reduced pressure to dryness.

The extract was dissolved in alcohol, mixed with silica gel, evaporated to dryness, and baked for 3−4 h at 60 ℃. Cordycepin was separated by a GF254 SIL column (9 cm × 60 cm) with the mobile phase of petroleum ether / dichloromethane/methanol (1.5 : 3 : 0.6). Samples were collected (500 mL of each fraction) and traced by TLC, with the cordycepin reference substance (Sigma) as a control. The fraction with cordycepin was concentrated under reduced pressure to dryness and recrystallized with ethanol. Light yellow or white crystal was collected and identified as 3'-deoxyadenosine (cordycepin) by chromatographic analysis (NMR, MS) and element analysis with a purity of ≥ 98% (HPLC).

Animals   In these experiments, we followed the Guidelines for Care and Use of Laboratory Animals as approved by Chinese Academy of Medical Sciences & Peking Union Medical College. Male Syrian golden hamsters with an initial body weight of (85 ± 10) g, and male Wistar rats with an initial body weight of (160 ± 20) g and ICR mice with initial body weight of (20 ± 2) g purchased from Institute of Experimental Animals, Chinese Academy of Medical Sciences & Peking Union Medical College were used in this study. They were housed in a regulated environment (22 ± 2) ℃, with a 12 h dark and 12 h light cycle (08 : 00−20 : 00, light). With regard to changes in body weight, no statistically significant differences existed among the control and the sample-treated animals during the experimental period.

High-fat diet induced hyperlipidemic model in hamsters and rats   Hyperlipidemic model was induced by feeding with high-fat diet. Normal basal diet contains 20% wheat flour, 10% rice flour, 20% corn, 20% bean, 25% wheat bran, 2% bone powder and 2% fish powder. The high-fat diet was prepared by mixing with the normal basal diet. Dietary ingredients for hamster were 20% lard, 0.2% cholesterol and 79.8% normal basal diet, while dietary ingredients for rat were 10% lard, 4% cholesterol, 0.2% propylthiouracilum and 85.8% basal normal diet (*w/w*).

Animal grouping and drug administration After the animals were accustomed for one week, blood was collected from orbit vein for assaying the content of serum total cholesterol and triglyceride for grouping. The hamsters or rats were divided into the following groups with eight animals per group respectively, accounted into their body weight and the levels of serum total cholesterol and triglyceride, which were normal control group, hyperlipidemic model group, fenofibrate (40 mg·kg^{-1}, purity $\geqslant$ 99%, powder, Sigma) group as a positive control[10], cordycepin low dose group (12.5 mg·kg^{-1}), cordycepin middle dose group (25 mg·kg^{-1}) and cordycepin high dose group (50 mg·kg^{-1}). The animals in normal control group were fed with ordinary diet, and those in hyperlipidemic model group were fed with high-fat diet *ad libitum* for 4 weeks. Meanwhile, the indicated drugs were given by oral gavage once daily (from 8 to 9 am).

Cordycepin, extracted from *Cordyceps militaris*, was dissolved in distilled water prior to administration. The animals in the normal control and in the hyperlipidemic model control group received a same volume of distilled water as those of the drug-treated groups.

Measurement of body weight   Body weight of these animals was measured on days 0 and 28 in the experiment. To reduce the error originated from feeding, all animals were fasted (water was not restricted) for 12 h before measurement.

Blood sampling and processing   At the end of experiment period, after fasting for 12 h, the animals were anesthetised with ethyl ether and blood was collected from orbit vein for serum preparation. Animals were heparinized by injection of heparin at dose of 100 u·kg^{-1} through tail vein, then within 15 min blood was then drawn from abdominal aorta for assaying the activity of HL and that of LPL.

Measurement of serum cholesterol and triglyceride levels   Levels of TC, TG, LDL-C and HDL-C in serum were determined by enzymatic colorimetic methods using commercial kits (Zhongshen Biotechnogical Co, Ltd. Beijing, China). The concentration of very low density lipoprotein cholesterol (VLDL-C) was calculated by the following equations according to the methods of Fridewald formula calculation [11].

Determination of plasma HL and LPL activity The activity of HL and LPL were determined by enzymatic method. Test kits were purchased from Jiancheng (Bioengineering Co., Ltd. Nanjing, China).

Determination of acute toxicity with ICR mice Based on the maximum dose approach, twenty mice, half male and half female, were selected and dosed intragastrically with the maximum dose of cordycepin (5 g·kg^{-1}). Observation is to be conducted after dosing for the animals' toxicity symptoms and time, extent, development, features in two weeks. Dissection is to be made and observation for change of the main organs is to be conducted.

Statistical analyses   Data are presented as the mean ± SD. One-way ANOVA was used to determine significant differences among groups, after which the modified Student's *t*-test with the Bonferroni correction was used for comparison between individual groups. $P < 0.05$ was considered statistically significant.

Results

1 Cordycepin doesn't affect the body weight of the hamsters and rats

There was no difference in weight of the hamster or rats in different treatment groups at baseline (Table 1). After 28 days of feeding with high fat diet and cordycepin administration, there was still no significant difference among the body weight.

2 Cordycepin reduces the serum lipid contents of the high-fat diet fed hamsters and rats

Untreated animals exposed to hight-fat diet for

Table 1   Effect of cordycepin (CCS) on hamsters' and rats' body weight. $n = 8$, $\bar{x} \pm s$

Group	Dose /mg·kg^{-1}	Body weight/g			
		Rat		Golden hamster	
		0 day	28 day	0 day	28 day
Control	–	185 ± 7	232 ± 12	108 ± 19	115 ± 15
Model	–	183 ± 12	221 ± 14	107 ± 17	118 ± 20
Fenofibrate	40	182 ± 12	219 ± 19	107 ± 12	130 ± 21
CCS	12.5	182 ± 11	220 ± 8	107 ± 8	118 ± 8
	25	183 ± 8	213 ± 17	105 ± 15	114 ± 15
	50	184 ± 12	226 ± 21	108 ± 13	121 ± 32

4 weeks, which served as model group, obviously developed hypercholesterolemia compared with that in normal control. Besides, fenofibrate, the positive agent, markedly reduced the levels of TC, TG, LDL-C, VLDL-C levels in hyperlipdemic hamsters, implicating that the experimental system has been confirmed to be successful.

Noticeably, cordycepin significantly decreased serum TG, LDL-C and VLDL-C levels in the hyperlipidemic hamsters, slightly reduced TC contents (shown in Figure 1). Similar results were observed in the hyperlipidemic rat model (shown in Figure 2). These data indicated that cordycepin potently lowered plasma lipids *in vivo*.

There was no significant difference among HDL-C levels in any groups (data were not shown). However, both LDL-C/HDL-C and TC/HDL-C were obviously higher in hyperlipidemic model group than those observed in control group. Cordycepin at the indicated doses of 12.5 to 50 mg·kg^{-1} potently reduced the LDL-C/HDL-C and TC/HDL-C levels in hyperlipidemic hamsters and bore a similarity in potency to the effect afforded by fenofibrate at dose of 40 mg·kg^{-1} (shown in Figure 3). Cordycepin at the indicated dose of 50 mg·kg^{-1} potently reduced the LDL-C/HDL-C levels in hyperlipidemic rats, but there was no significant difference in TC/HDL-C levels compared with model group when treated with cordycepin (shown in Figure 4).

3　Cordycepin increases the activity of plasma HL and LPL of the high-fat diet fed hamsters and rats

Four-week high-fat diet decreased the plasma activities of both HL and LPL significantly in the two animal models. The presence of cordycepin at dose of 50 mg·kg^{-1} significantly activated the enzymes, while no obvious changes were observed in the middle-dose or the low-dose group of the hamsters. The presence of cordycepin at dose of 50, 25, 12.5 mg·kg^{-1} in rats significantly activated the enzymes (shown in Table 2).

4　Cordycepin shows good biological safety in the acute toxicity test

After 20 mice were treated with solution of cordycepin at dose of 5 g·kg^{-1}, the animals were observed for 14 days, during which time no obvious toxicity symptoms or death was found in the mice. Mice acted as normal and didn't show much difference in its activity compared with before, the animal hair didn't have any significant change, either. The acute toxicity test on mice did not show any sign in net body weight gain, food and water consumptions, organ weights, *etc.*
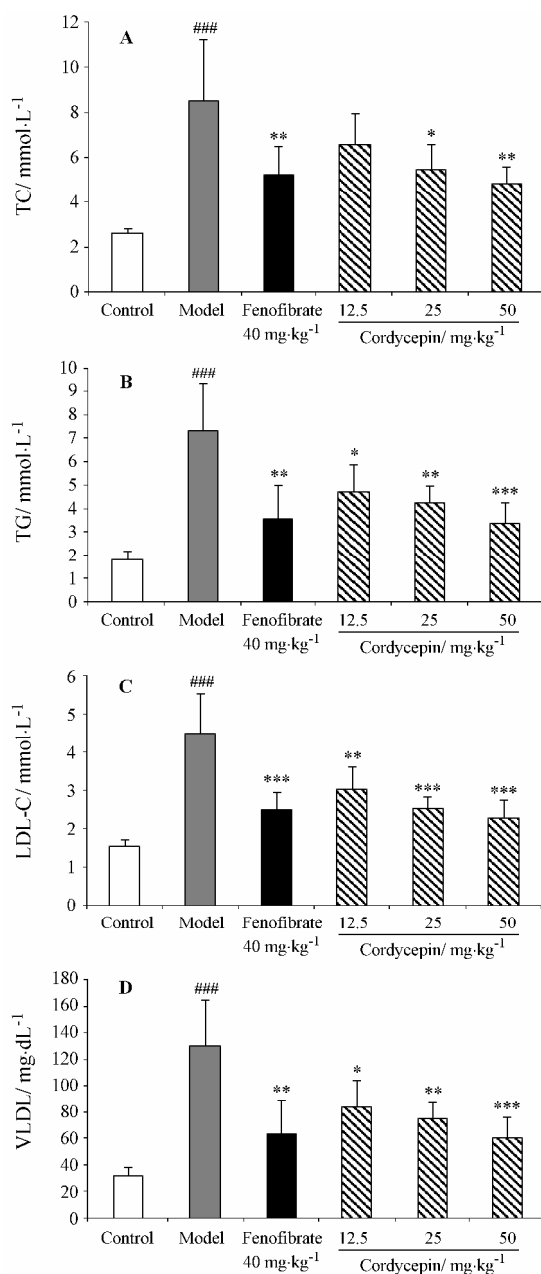

Figure 1　Effects of cordycepin on the serum lipid profile in hyperlipidemic hamsters. The serum lipid levels of the experimental animals are described. The high-fat diet resulted in significant increasing of serum lipids including the total cholesterol (TC), triglyceride (TG) and low density lipoprotein cholesterol (LDL-C). TC (A), TG (B), LDL-C (C) and very low density lipoprotein cholesterol (VLDL-C, D) separately were significantly decreased by cordycepin compared with the high-fat diet group. $^{###}P < 0.001$ *vs* control group; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* high-fat diet group. Data are expressed as the mean ± SD. $n = 8$

Discussion

Cordycepin is a nucleoside derivative, 3'-deoxyadenosine, found in fungi of the genus cordyceps. As early as in the 1950s, a compound from *Cordyceps*
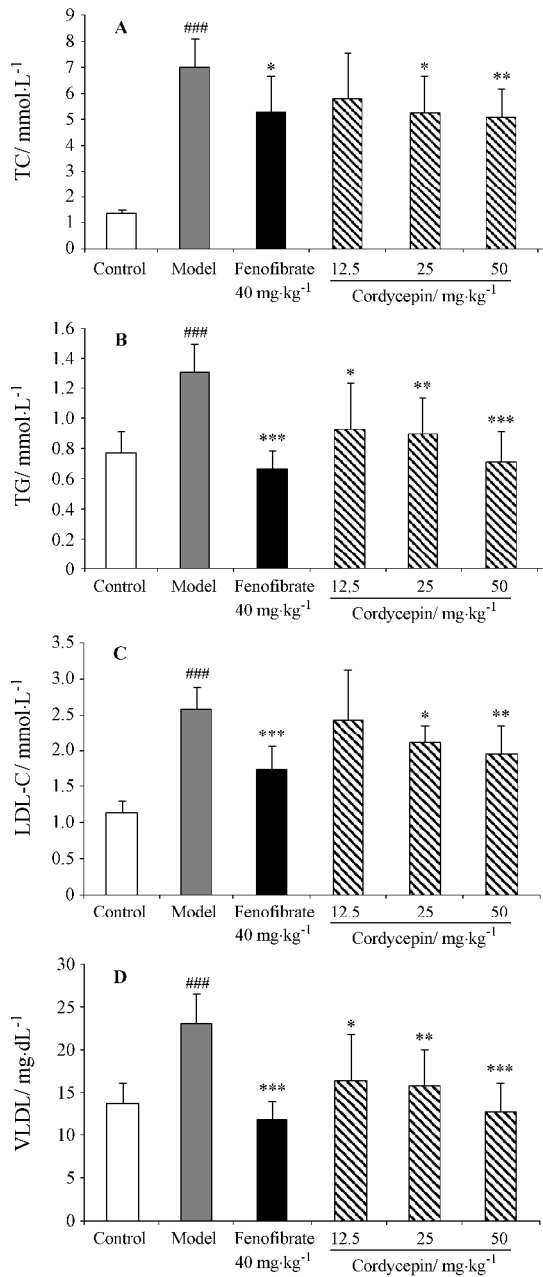
Figure 2 Effects of cordycepin on the serum lipid profile in hyperlipidemic rats. The serum lipid levels of the experimental animals are described. The high-fat diet resulted in significant increasing of serum lipids including the TC, TG and LDL-C. TC (A), TG (B), LDL-C (C) and VLDL (D) separately were significantly decreased by cordycepin compared with the high fat diet group. [###]$P < 0.001$ *vs* control group; [*]$P < 0.05$, [**]$P < 0.01$, [***]$P < 0.001$ *vs* high-fat diet group. Data are expressed as the mean $\pm$ SD. $n = 8$

militaris was isolated to inhibit growth of *Bacillius subtilis*, which was later identified as cordycepin (3'-deoxyadenosine)[12]. Since then, multiple-biological effects have been attributed to cordycepin, such as anti-fungal activity[13], anti-malarial activity[14], anti-herpes activity[15], anti-tumor[16, 17] and anti-aumrigenic activity[18]
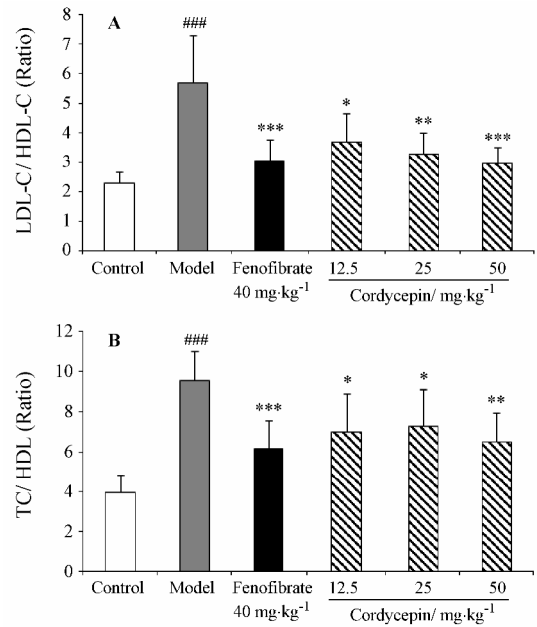
Figure 3 Effects of cordycepin on LDL-C/HDL-C and TC/HDL-C ratios in hamsters. Two indexes: LDL-C/HDL-C and TC/HDL-C are shown. The concentrations of indexes in hamsters of the high-fat diet group were significant different compared with those in the control group. LDL-C/HDL-C ratios (A) and TC/HDL-C ratios (B) were significantly lower in the hamsters administrated with cordycepin than the hamsters in the high-fat diet group. [###]$P < 0.001$ *vs* control group; [*]$P < 0.05$, [**]$P < 0.01$, [***]$P < 0.001$ *vs* high-fat diet group. Data are expressed as the mean $\pm$ SD. $n = 8$
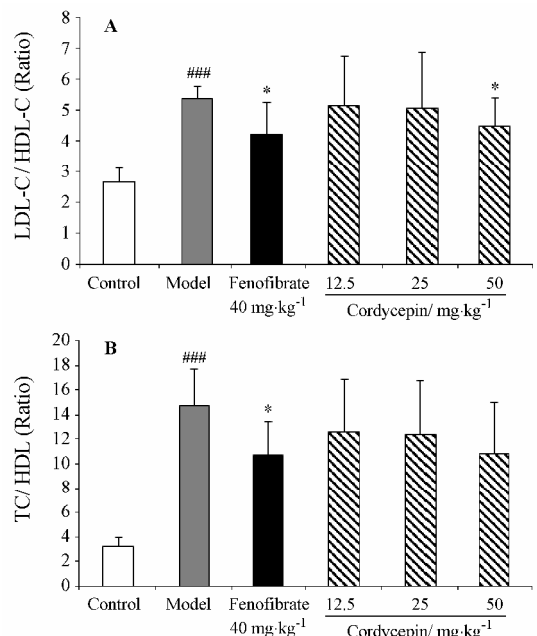
Figure 4 Effects of cordycepin on LDL-C/HDL-C and TC/HDL-C ratios in rats. Two indexes: LDL-C/HDL-C and TC/HDL-C are shown. The concentrations of indexes in rats of the high-fat diet group were significant different compared with those in the control group. LDL-C/HDL-C ratios (A) were significantly lower in the rats administrated with cordycepin of 50 mg·kg^{-1} than those in the high-fat diet group. TC/HDL-C ratios (B) were lower in the rats administrated with cordycepin than those in the high-fat diet group, but without significant difference. [###]$P < 0.001$ *vs* control group; [*]$P < 0.05$ *vs* high-fat diet group. Data are expressed as the mean $\pm$ SD. $n = 8$

Table 2　Effect of cordycepin on hamsters' and rats' plasma HL and LPL activity.　　$n = 8$, $\bar{x} \pm s$.　[#]$P < 0.05$, [##]$P < 0.01$, [###]$P < 0.001$ *vs* control group; [*]$P < 0.05$, [**]$P < 0.01$ *vs* model group

Group	Dose /mg·kg^{-1}	Rat		Golden hamster	
		HL /u·mL^{-1}h^{-1}	LPL /u·mL^{-1}h^{-1}	HL /u·mL^{-1}h^{-1}	LPL /u·mL^{-1}h^{-1}
Control	−	3.03 ± 0.69	0.81 ± 0.26	2.99 ± 0.53	2.18 ± 0.53
Model	−	1.63 ± 0.69[##]	0.48 ± 0.19[#]	1.71 ± 0.61[###]	1.15 ± 0.54[##]
Fenofibrate	40	2.77 ± 0.78[*]	0.87 ± 0.32[*]	2.7 ± 0.73[*]	2.12 ± 0.65[**]
CCS	12.5	2.55 ± 0.62[*]	0.88 ± 0.25[**]	1.88 ± 0.62	1.12 ± 0.4
	25	2.68 ± 0.9[*]	0.85 ± 0.2[**]	1.93 ± 0.84	1.35 ± 0.6
	50	2.93 ± 0.97[**]	0.92 ± 0.33[**]	2.64 ± 0.63[*]	1.78 ± 0.6[*]

on some cell lines, stimulating effect on interleukin-10 production as a immune-modulator as well as anti-inflammation.　However, little has been known about hypolipidemic activity of cordycepin so far.　In order to identify the treatment for dyslipidemia with this fungus that are responsible for its putative clinical effects, cordycepin, pure compound from *Cordyceps militaris* was evaluated by *in vivo* study.

Hamster possesses many similar features in cholesterol metabolism compared to humans[19], while high-fat diet fed Wistar rat is commonly used in lipid lowering studies[20].　In this research, we used male Golden Syrian hamster and Wistar rat, which were fed with high-fat diet, to study the lipid lowering effect of cordycepin.　After 28 days of dietary fat manipulations, the levels of serum lipids elevated in hyperlipidemic model group of both hamsters and rats compared with those observed in the control group (Figure 2, Figure 3).　Therefore, they are considered to be useful rodent models for studying hyperlipidemia.

Our results provided the evidence for the hypolipidemic effects of cordycepin by lowering LDL-C and TG and increasing the activities of HL and LPL.　No significant difference in body weight was found in the indicated groups fed with high-fat diet for 4 week, which was in consistent of previous report[21].

Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions[22].　Our data implicated that an increase in total cholesterol in hyperlipidemia hamsters and rats are due to the rise in LDL and triglycerides levels.　In addition, an increase of serum TG is also considered to be an important risk factor for atherosclerosis.　Elevated levels of plasma TG, LDL-C and VLDL, accompanied by reduced HDL-C levels, are important risk factors for atherosclerosis, besides, they are usually associated with an increased risk of coronary heart disease. Studies have demonstrated that LDL-C is the most dangerous factor among the serum lipids[23, 24].　Present results clearly show that

the cordycepin at a dose of 50, 25, and 12.5 mg·kg^{-1} significantly lowered plasma triglycerides and LDL-C content, which is the target of several marketing hypolipidemic drugs, and did not affect plasma HDL-C level significantly.

VLDL is rapidly remodeled by LPL and metabolized to IDL (intermediate density lipoprotein), and finally converted to LDL.　The enhancement of VLDL clearance may arise from the active incorporation of IDL and LDL metabolized from VLDL into the liver[25].　The present study has shown that VLDL increased in hyperlipidemic model group, but the effect was reversed by oral administration of cordycepin or fenofibrate.　These results coincided with the increased effect on LPL activity by cordycepin.

The results of the earliest trials showed that modest reductions in total cholesterol and LDL-C were associated with reductions in fatal and nonfatal coronary heart disease events[26].　Risk of CHD is positively correlated with LDL-C, whereas it is inversely associated with HDL-C[27].　Our investigation showed that cordycepin exerted a potent effect on reduction of LDL-C/HDL-C index, which implies benefit effect on reduction of CHD events.　The administration of cordycepin reduced TC/HDL-C index in hyperlipidemic hamster, implicating that TC level was regulated by the presence of cordycepin.　These results imply that the effect of cordycepin on regulating lipid profile to benefit state in hyperlipidemic hamsters and rats might be due to affecting LDL-C level followed by reducing the ratio of LDL-C/HDL-C.

LPL, a triglyceride hydrolase, is responsible for hydrolysis of TG, resulting in free fatty acids taken up and utilized by the adjacent tissues.　HL processes the remnants hydrolysed by LPL interactive with apoE and reduce the triglyceride content[28].　The LPL and HL decreased in hyperlipidemic model group and improved by the presence of cordycepin at dose of 50 mg·kg^{-1} or fenofibrate at dose of 40 mg·kg^{-1} in hamsters; at

the same time, they were improved by the presence of cordycepin at dose of 50, 25 and 12.5 mg·kg^{-1} or fenofibrate at dose of 40 mg·kg^{-1} in rats. However, how the LPL and HL participate in the reduction of LDL-C level needs further study.

The results ensure us to conclude that cordycepin has pronounced lipid-lowering effects on the hyperlipidemic hamsters and rats. The intake of cordycepin could decrease the levels of serum TG, serum TC, LDL-C and VLDL-C as well as increase the activity of hepatic lipase and lipoprotein lipase. The data suggested that the lipid-lowering actions of cordycepin are attributed to its ability to modulate lipid metabolism. Importantly, no obvious acute toxicity of cordycepin was found in mice. Therefore, cordycepin (3'-deoxyadenosine) might be a potential agent for treatment of hyperlipidemia.

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