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The anti-hyperglycemic activity of the fruiting body of Cordyceps in diabetic rats induced by nicotinamide and streptozotocin

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Abstract

Little scientific evidence exists to support the numerous herbs used to improve diabetes-related metabolic disorders. Cordyceps, a Chinese herbal medicine with fruiting body and carcass, has been proposed to have multiple medicinal activities. The objective of this study was to investigate the effects of fruiting body and carcass of Cordyceps on hyperglycemia. Male Wistar rats administered with placebo (STZ group), 1 g of fruiting body (FB group), 1 g of carcass (CC group), or 1g of fruiting body plus carcass (CF group) of Cordyceps for four weeks (d1 to d28) were injected with nicotinamide (200 mg/kg) and streptozotocin (65 mg/kg) on d15. Animals fed with placebo and injected with saline acted as the controls (CON group). The results showed that water intake (d15 to d29), changes in fasting blood glucose concentration (d15 to d26), and serum concentrations of fructosamine (d29) were significantly greater in the STZ, CC and CF groups than in the CON and FB groups (one-way ANOVA, $P < 0.05$). The diabetic rats had significantly lower weight gain and higher blood glucose response in oral glucose tolerance test than the control rats; and these changes were significantly reduced by administrating the fruiting body of Cordyceps. Our results revealed that fruiting body, not carcass, of Cordyceps attenuated the diabetes-induced weight loss, polydipsia and hyperglycemia, and these improvements suggest that fruiting body of Cordyceps has a potential to be the functional food for diabetes.

Keywords: Anti-hyperglycemic activity; Cordyceps; Diabetes; OGTT; Fructosamine

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Introduction

Type 2 Diabetes mellitus (DM), a metabolic disease characterized by hyperglycemia and dyslipidemia resulting from defects in both insulin secretion and insulin resistance, has been a significant growing problem in both developed and developing countries (Heine, 1999). In recent years, the medical cost for specific diabetes-related complications and long-term effects is greater than that of other diseases (Jonsson, 2002; Ashton et al., 2003). Most type 2 diabetic patients, who have abnormal nutrient metabolism and hormonal regulations, require oral hypoglycemic medicines or exogenous insulin injections to maintain glucose homeostasis and to reduce the development of micro- and macro-vascular diseases (Modena and Barbieri, 1999). Nevertheless, it is common that people who have a degree of hyperglycemia sufficient to cause pathological and functional changes, remain undetected for a long period of time before diabetes is diagnosed. After a challenge with an oral glucose load, such as oral glucose tolerance test (OGTT), people who have abnormal carbohydrate metabolism can more easily to be identified in this asymptomatic period. Therefore, the present focus on diabetes management turns to the prevention of diabetes and its complications (Unwin et al., 2002).

In traditional Chinese medicine, several herbs have been used to improve the hyperglycemic condition in DM patients (Kiho et al., 1993, 1995, 1996, 1997, 1999; Kamtchouing et al., 1998). Cordyceps, so called "winter-worm and summer-grass" which is composed of a parasitic fungus of *Cordyceps sp.* and its host, the larva of *Hepialus armoricanus* Oberthur, is well known crucial nourishing tonic and has been used as a treatment for many ailments for hundreds of years (Halpern, 1999). According to ancient descriptions of Chinese herbs, Cordyceps possesses important pharmacological activities in protecting lung and kidney functions and in nourishing the essence and vital energy (Tsunoo et al., 1995). In addition, historically in Chinese Medicine it is believed that the fruiting body and carcass of Cordyceps may maintain the "Yang" and "Yin" of the body, respectively. Recent scientific evidences have shown that Cordyceps is capable of modulating immune response (Kiho et al., 1992), inhibiting tumor growth (Ohmori et al., 1989; Kuo et al., 1994; Yoshida et al., 1989), and improving hyperlipidemia, hyperglycemia, and sexual function (Kiho et al., 1993, 1996, 1999). However, there has been no study to demonstrate whether the fruiting body and carcass of Cordyceps have different biological activities.

Polysaccharides extracted from cultured mycelium of Cordyceps and administered intraperitoneally showed potent hypoglycemic activity in genetic diabetic mice. Also, plasma glucose levels were acutely reduced in normal and streptozotocin-induced diabetic mice via intravenous administration (Kiho et al., 1993, 1996, 1999). There is little information regarding enteral feeding of the natural product of Cordyceps as a functional food to improve glycemic condition in diabetes. Using a nicotinamide and streptozotocin-induced diabetic rat model, we investigated the effects of orally administered fruiting body and carcass of Cordyceps on hyperglycemia. To fulfill the practical role of functional food as an agent to prevent and attenuate, rather than to treat or cure, the disease, rats were administered with Cordyceps prior to the induction of diabetes. The purposes of this study were to investigate whether there is different biological activity in the fruiting body and carcass of Cordyceps, and to provide evidence for promoting Cordyceps as a functional food with anti-hyperglycemic activity.

Materials and methods

Animals and experimental design

The animal facilities and protocol were approved by the Laboratory Animal Care and Use Committee at Changhua Christian Hospital, Changhua, Taiwan. Male Wistar rats (Animal Center of National Taiwan University, Taipei, Taiwan) weighing around 200 g were housed in individual stainless steel cages with free access to water in a room maintained at 22 °C on a 12:12-hour light-dark cycle. Five days prior to the experiment, animals were trained to eat a semi-purified powdered diet (AIN-76, ICN biomedicals Inc.) from 0900h to 1700h and this eating schedule was maintained during the experimental period. Total calories of the powdered diet composed of 21%, 67.4%, and 11.6% of protein, carbohydrate, and fat, respectively. After adapting to the animal facility for 5 days, the fasting blood was collected via tail vein puncture to measure the blood glucose concentration, then animals were randomly divided into five groups (d1).

In the morning of d1 to d28, the animals were fed with 5 g of semi-purified powdered diet mixed with 1 g of the fruiting body (FB group), carcass (CC group), or fruiting body plus carcass (CF group) of Chinese herbal medicine Cordyceps, purchased from a Chinese medicine store (Sun Ten Pharmaceutical Co., Taipei, Taiwan), or 5 g of diet mixed with 0.3 g of starch plus 0.2 g of cellulose (CON and STZ groups), which has similar amounts of carbohydrate and fiber as 1 g of Cordyceps (Shiao et al., 1989). As the mixed diet was completely consumed, animals were fed with semi-purified powdered diet in the rest of day, and then they were fasted from 1700h to 0800h. The amount of diet consumed was measured daily as the spilled diet was collected and measured. Meanwhile, the daily water consumption and weekly body weight were recorded.

On d15, animals in the FB, CC, CF and STZ groups (n = 12/group) were intra-peritoneally administered with 200 mg nicotinamide per kg of body weight. Fifteen minutes later, animals under light ether anesthesia were administered with 65 mg streptozotocin (Sigma Chemical Co., St. Louis, MO) per kg of body weight via tail vein injection to introduce diabetes (Masiello et al., 1998). The order in which the animals were injected was randomized among the groups. In addition, the intra-peritoneal and intravenous injections were performed thoroughly by two investigators without identifying the animal group. Nicotinamide was dissolved in a saline buffer, streptozotocin was dissolved in a 0.01M citric saline buffer (pH 4.5), and both were filtrated through a disposable 0.22 μm sterile filter unit (Millex-GS, Millipore Co., Bedford, MA) immediately before injection. Animals in the CON group were intra-peritoneally and intravenously administered with saline (n = 8).

After overnight fasting on d26, the oral glucose tolerance test (OGTT) was performed on the animals. Glucose (2g/kg body weight) was intragastrically administered as a 30% solution to animals. Blood samples were collected sequentially from the tail vein before, and 10, 20, 30, 60, 90, and 120 min after the glucose administration. During the experimental period, the fasting blood glucose concentrations were measured on d1, d15, d22, d26 and d29.

On d29, animals were sacrificed under anesthesia with intramuscular injections of 100 mg ketamine and 10 mg xylazine per kg of body weight. The order in which the animals were sacrificed was randomized among the groups. Blood was collected by cardiac puncture and the serum and whole blood were isolated for different assays. Liver, heart, lung, thymus, spleen, kidney, pancreas, and gastrocnemius muscles were dissected, and their weights were recorded. The pancreas was put in liquid N immediately and stored at −80 °C until analysis for insulin. The entire gastrointestinal tract was

removed from each animal, and the weight of the small intestine was determined after removing the gut contents and rinsing with cold saline. The animal carcass weights were recorded without the above organs and tissues and were stored at $-20\,^{\circ}C$ until analysis of body composition.

Analytical measurements

The fasting blood glucose concentration was determined using MediSense Card Blood Glucose Testing Systems (PrecisionPlus Electrodes, Abbott Laboratories, Bedford, MA), which uses an electrochemical detection technique with a glucose oxidase method. One day before the fasting blood glucose levels were measured, the postprandial urinary levels of ketone bodies, glucose and protein, the pH values, and the presence of blood were determined using multiple test strips (Uriscan strip, Yeongdong Pharmaceutical Corp., Seoul, Korea). Complete blood counts, including the levels of red blood cells, white blood cells, hemoglobin, hematocrit, and platelet, were measured using a hematology analyzer (GEN'S, Coulter Inc., FL). Serum concentrations of albumin, cholesterol, triglyceride, creatinine, blood urea nitrogen (BUN), and uric acid were measured by an automatic analyzer (Hitachi 747, Japan).

Serum concentrations of free fatty acid and fructosamine were determined by enzymatic colorimetric assays (Boehringer Mannheim, Philadelphia, PA, and Sigma Chemical Co., Louis, MO), and the insulin concentrations in the serum and pancreas were measured by commercially available enzyme-linked immunosorbant assays (ELISA; American Laboratory Products Company, Ltd., Windham, NH). The pancreatic insulin was extracted by hydrochloride-acidified ethanol, as described by Masiello et al (Masiello et al., 1998), prior to measuring the insulin. All the samples were analyzed in one assay in duplicate with intra-assay coefficients of variation below 10%.

Animal carcass compositions, such as percentage and amount of water, protein, and fat, were measured with methods as previously described (Yang et al., 1994). In brief, total carcass water was determined by freeze-drying the carcasses for 2 weeks to obtain a dried carcass weight and then subtracting the dried carcass weight from the total carcass weight. The freeze-dried carcasses were then homogenized with liquid nitrogen, and aliquots of dried rat homogenate were assayed for nitrogen and fat concentrations. The carcass fat concentration was determined by extracting dried rat homogenate with ether, and then evaporating the ether to determine the fat amount. In addition, carcass nitrogen concentration was determined by micro-Kjeldahl analysis.

Statistical analysis

All treatment groups were compared by one-way analysis of variance (ANOVA) using the SAS general linear models program. Values were reported as means $\pm$ SEM. Group means were considered to be significantly different at $P < 0.05$, as determined by the technique of protective least-significant difference (LSD) when the ANOVA indicated an overall significant treatment effect, $P < 0.05$.

Results

The daily body weight and body weight gains are shown in Fig. 1. There was no significant difference in body weight among the groups during the experimental period. However, body weight gains from d15

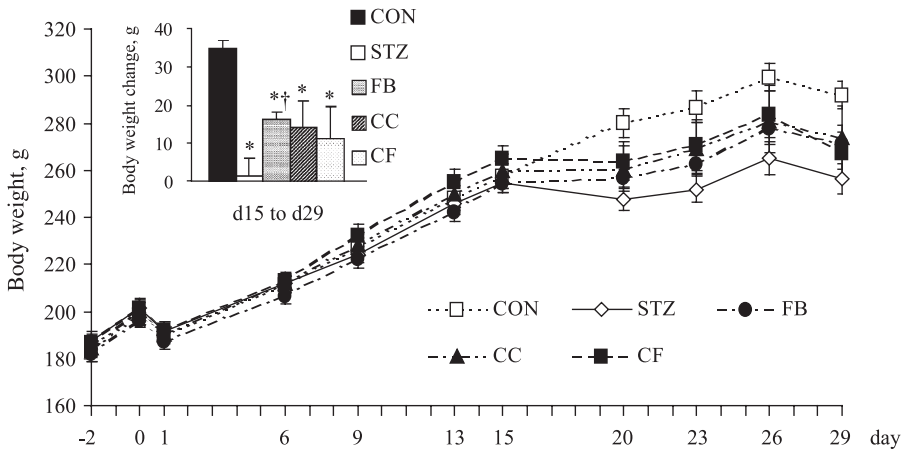

Fig. 1. Daily body weight and body weight change (d15 to d29, see insert) in rats administered with or without Cordyceps. Values are means ± SEM, n = 8 for the CON group and n = 12 for the other groups. Values with symbol * are different from the CON group and with symbol † are different from the STZ group, $P < 0.05$.

to d29 were significantly lower in diabetic animals, i.e., the STZ, FB, CC and CF groups, than in nondiabetic animals, i.e., the CON group. In addition, animals in the FB group had significantly greater body weight gains than those in the STZ group. There were no significant differences in food intake during the experimental period, and in water intake before the streptozotocin injection among the groups. After streptozotocin was injected, the diabetic animals had a significantly increased water intake when compared with the nondiabetic animals. Oral administration of the fruiting body of Cordyceps significantly attenuated the increased water intake in diabetic animals. The levels of ketone bodies

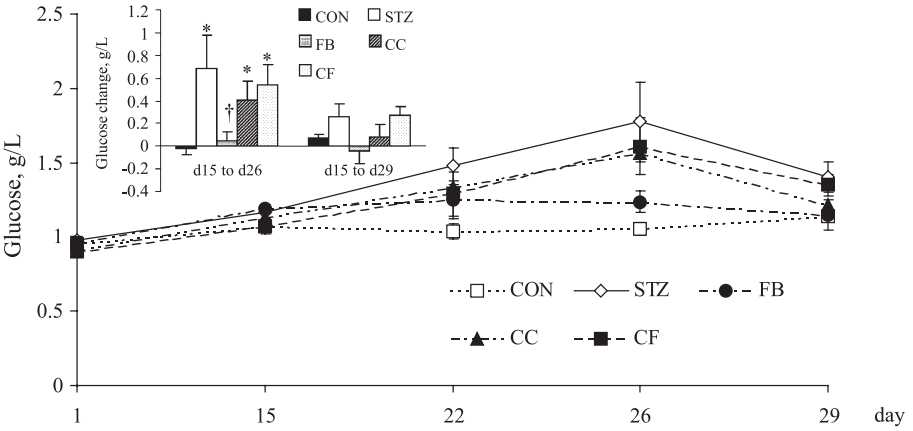

Fig. 2. Fasting blood glucose concentrations during the experimental period and changes in fasting blood glucose concentrations (see insert) from d15 to d26, i.e., 10 days after STZ injection, and from d15 to d29, i.e., 14 days after STZ injection, in rats administered with or without Cordyceps. Values are means ± SEM, n = 8 for the CON group and n = 12 for the other groups. Values with symbol * are significantly different from the CON group and with symbol † are significantly different from the STZ group, $P < 0.05$.

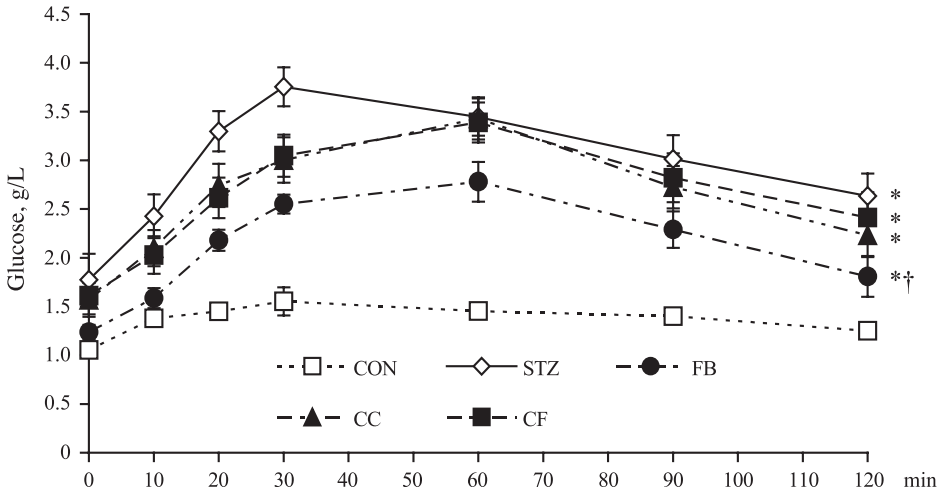

Fig. 3. Blood glucose concentrations of the OGTT (2 g glucose per kg of body of body weight) on d26 in rats administered with or without Cordyceps. Values are means ± SEM, n = 8 for the CON group and n = 12 for the other groups. There was no significant difference at baseline (0 min) among the groups. Symbols * and † indicate significant differences to the CON and STZ groups, respectively, from 10 to 120 min during the OGTT, $P < 0.05$.

and protein and pH values in the urine were not significantly different among the groups during the experimental period. No animal had bloody urine in each group. However, all of the diabetic animals had a significant glucose response in the urine after streptozotocin was injected. The urinary glucose response was negative in the nondiabetic group.

Fasting blood glucose concentrations were not significantly different among the groups during the experimental period (Fig. 2), but it was tended, though not statistically significant, to be lower in the CON group than in the STZ group on d26 ($P = 0.062$). In order to account for the individual differences

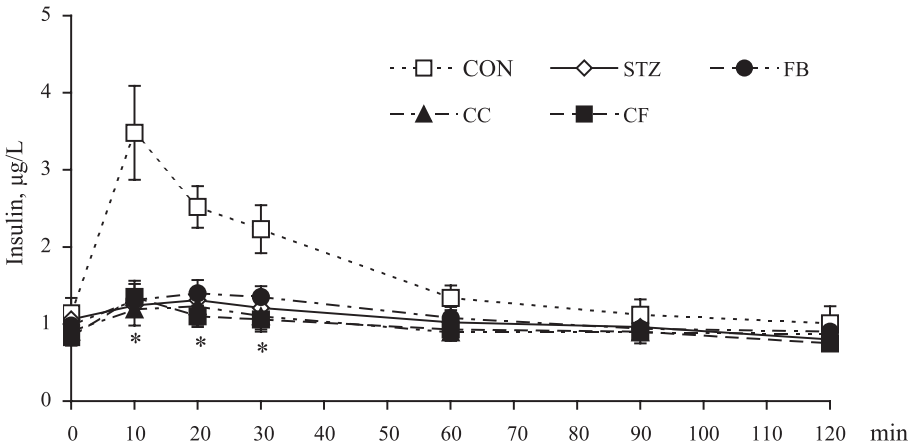

Fig. 4. Serum insulin concentrations of the OGTT (2 g glucose/kg body of body weight) on d26 in rats administered with or without Cordyceps. Values are means ± SEM, n = 8 for the CON group and n = 12 for the other groups. Values with symbol * are different from the CON group at 10, 20, and 30 min in the OGTT, $P < 0.05$.

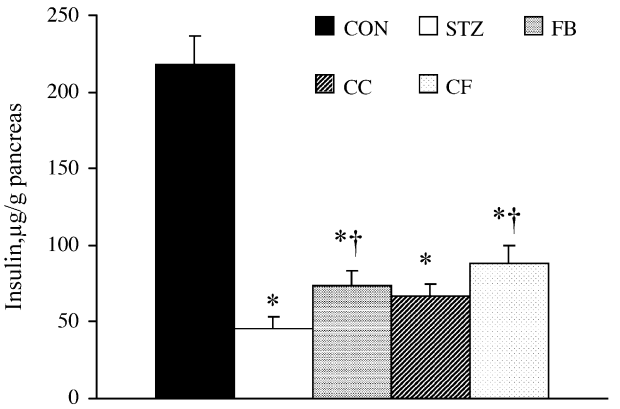

Fig. 5. Insulin content of the pancreas. Values are means ± SEM, n = 8 for the CON group and n = 12 for the other groups. Values with symbol * are different from the CON group and with symbol † are different from the STZ group, P < 0.05.

among rats, we calculated the change in fasting blood glucose concentrations to investigate the effect of Cordyceps on blood glucose. The changes in fasting blood glucose concentrations from d15 to d26 were significantly higher in the STZ, CC and CF groups than in the CON group (the insert of Fig. 2); whereas it was significantly lower in the FB group than in the STZ group. The changes in blood glucose from d15 to d29 had a similar pattern as that from d15 to d26, but this was not statistically significant. There were no significant differences in serum insulin concentration among the groups during the experimental period (data not shown).

The results of OGTT are shown in Fig. 3. Among the groups, the concentrations of blood glucose baseline (0 min) were not significantly different, and the diabetic animals had significantly higher blood glucose concentrations than the nondiabetic animals from 10 to 120 min during the OGTT. Furthermore, animals in the FB group had significantly lower blood glucose concentrations than those in the STZ group from 10 to 120 min during the OGTT. The insulin concentrations were significantly lower in the diabetic groups when compared with the nondiabetic group at 10, 20, and 30 min during the OGTT (Fig. 4). There was no significant difference in serum insulin concentrations between the diabetic and nondiabetic rats at baseline and at 60, 90, and 120 min during the OGTT. The insulin contents per gram of pancreas were significantly decreased in the diabetic groups when compared with the nondiabetic group (Fig. 5). The FB and CF groups had significantly increased insulin content in the pancreas when compared with the STZ group.

Table 1
Serum substrate concentrations in rats administered with or without Cordyceps[1]

Group	Albumin g/L	Triglyceride mg/L	Cholesterol mg/L	Creatinine mg/L	BUN mg/L	Fructosamine mmole/L
CON	42.6 ± 0.7	396.3 ± 37.5	595.0 ± 19.5	3.88 ± 0.13	160.6 ± 8.8	1.654 ± 0.066
STZ	40.4 ± 0.8	402.0 ± 37.6	699.0 ± 33.8	4.50 ± 0.17*	173.3 ± 11.2	2.245 ± 0.163*
FB	42.1 ± 0.7	431.1 ± 40.6	620.0 ± 41.5	4.89 ± 0.11*	161.2 ± 8.5	1.685 ± 0.095†
CC	41.1 ± 0.7	436.7 ± 59.4	659.2 ± 47.4	4.92 ± 0.08*†	171.8 ± 9.0	1.918 ± 0.074*
CF	40.6 ± 0.7	402.0 ± 47.7	628.0 ± 23.3	5.10 ± 0.18*†	167.5 ± 9.5	1.934 ± 0.162*

[1] Values are means ± SEM, n = 8 for the CON group and n = 12 for the other groups. Values in each column with symbol * are different from the CON group and with symbol † are different from the STZ group, P < 0.05.

Table 2
The tissue and organ weights in rats administered with or without Cordyceps[1]

Group	Liver g	Lung g	Kidney g	Thymus g	Pancreas g	Muscle[2] g
CON	7.90 ± 0.24	1.59 ± 0.05	2.08 ± 0.08	0.46 ± 0.03	1.37 ± 0.12	3.95 ± 0.11
STZ	7.86 ± 0.25	1.44 ± 0.05	2.11 ± 0.07	0.39 ± 0.02	1.15 ± 0.19	3.51 ± 0.08
FB	8.51 ± 0.29	1.51 ± 0.07	2.28 ± 0.07	0.48 ± 0.02†	1.24 ± 0.09	3.57 ± 0.06
CC	8.47 ± 0.35	1.59 ± 0.08	2.38 ± 0.11*†	0.40 ± 0.04	1.38 ± 0.09	3.74 ± 0.17
CF	8.79 ± 0.37	1.59 ± 0.08	2.40 ± 0.07*†	0.46 ± 0.03	1.29 ± 0.06	3.64 ± 0.13

[1] Values are means ± SEM, n = 8 for the CON group and n = 12 for the other groups. Values in each column with symbol * are different from the CON group and with symbol † are different from the STZ group, $P < 0.05$.

[2] The gastrocnemius muscle was used to represent the muscle.

The counts of red blood cell, white blood cell, and platelet were not significantly different among the groups (data not shown). Even though the hemoglobin level and hematocrit percentage were significantly decreased in the FB group (118 ± 1 g/L and 35.6 ± 0.4%) when compared with the STZ group (122 ± 1 g/L and 37.0 ± 0.5%), those values were not significantly different from that of the CON group. The serum substrate concentrations are listed in Table 1. There were no significant differences in serum concentrations of albumin, triglyceride, cholesterol, BUN, uric acid and free fatty acid among the groups. The diabetic animals had significantly increased serum concentration of creatinine when compared with the nondiabetic animals. Animals in the CC and CF groups had higher serum concentration of creatinine when compared with the STZ group. Serum concentrations of fructosamine were significantly increased in the STZ, CC and CF groups when compared with the CON group. Oral administration of fruiting body significantly attenuated the diabetes-induced increase in the concentration of fructosamine.

The weights of organ and tissue are listed in Table 2. There were no significant differences in the weights of liver, heart, lung, spleen, pancreas, small intestine and gastrocnemius muscle among the groups. The weight of kidneys were significantly increased in the CC and CF groups when compared with the CON and STZ groups. The weight of the thymus was significantly higher in the FB group when compared with the STZ group. The weights of animal carcass were not significantly different among the groups and the percentage and amounts of carcass water, protein, and fat were not significantly different among the groups (data not shown).

Discussion

It is known that considerable medical resources have been invested on the prevention and control of the diabetes-related complications. Even with diet and medical therapy, diabetic patients still have a high risk in developing the micro- and macro-vascular diseases. Lately, people with a family history of diabetes have been eager in finding a convenient approach to prevent or delay the occurrence of diabetes, thus the hypoglycemic functional food and nutraceuticals are extremely popular in the market. Cordyceps, which consists of the fungi parasite and its host insect, has been employed to treat various diseases by Chinese and other healthcare practitioners. This is the first study which demonstrated that the fruiting body, not carcass, of Cordyceps has a hypoglycemic activity in nicotinamide and streptozotocin-induced diabetic rats. Animals orally administered with the fruiting body of Cordyceps, had significantly

improved response in OGTT as well as significantly decreased serum fructosamine concentrations. In addition, the diabetes-induced increase in water consumption was attenuated by the fruiting body of Cordyceps. These results suggest that Cordyceps is a hypoglycemic functional food for diabetes.

There are various diabetic animal models which can be used to investigate the pathogenesis and evolution of diabetes and can possibly used to screen new anti-diabetic drugs, however, none of them is able to reproduce the complexity seen in human diabetes, especially type 2 DM. Streptozotocin, which is a specific cytotoxic agent for pancreatic β-cells, has been confirmed to have a diabetogenic action, and the intensity of the damage is graded according to the dosage used (Junod et al., 1969). By giving 230 mg of nicotinamide and 65 mg of streptozotocin per kg of body weight to adult rats, Masiello et al. had induced a diabetic syndrome with stable metabolic alterations and reduced pancreatic insulin stores which mimicked some features of type 2 DM (Masiello et al., 1998). In the present study, we used a similar nicotinamide and streptozotocin-induced diabetic rat model, which showed abnormal glucose tolerance and insulin responses but without significant body weight loss, to investigate the hypoglycemic activity of Cordyceps.

With little scientific evidence, numerous herbs have been used in alternative medicine to treat the diabetic related metabolic disorders. Recently, investigators demonstrated that polysaccharides, especially β-D-glucans, extracted from these herbs were the main bioactive ingredients with hypoglycemic activity. For example, the hot-water extracted polysaccharides of the fruiting bodies of Tremella aurantia (Kiho et al., 1995) and Pestalotiopsis species (Kiho et al., 1997) and the hot-water and alkaline extracted polysaccharides of the cultured mycelium of Cordyceps (Kiho et al., 1996) have hypoglycemic activity in normal, streptozotocin-induced diabetic (type 1 DM), or genetically diabetic (type 2 DM) mice following intravenous or intraperitoneal administration. In these studies the hypoglycemic activity of these herbal extracts were mostly tested via intravenous and intraperitoneal injections. Few studies have investigated the bioactivity of these crude herbal medicines via enteral administration and there is no study to report the effects of Cordyceps on whole body. Based on the definition of Zeisel on functional foods, which states ‘‘consumed as part of a normal diet and deliver one or more active ingredients within the food matrix’’ (Zeisel, 1999), we investigated the effects of orally administered Cordyceps as a functional food on blood glucose control as well as the total-body, organ and hematological responses in diabetic rats.

Kiho and colleagues reported that neutral polysaccharides (50 mg/kg), extracted from cultured mycelium of Cordyceps significantly decreased the plasma glucose in normal mice by oral administration (Kiho et al., 1993). Even though there is no available evidence, we believe that the other ingredients of natural Cordyceps, such as adenosine, cordycepin, amino acids, fatty acids, dietary fiber, vitamins, and minerals, may also have bioactivity in modulating carbohydrate metabolism. In addition, the different compositions of the fruiting body and carcass suggest that these two parts may have different bioactivities, as was recorded in the traditional Chinese medicinal book. Two recent studies demonstrated that a fermentation product of Cordyceps improved glucose metabolism and increased insulin sensitivity in normal rats (Zhao et al., 2002; Balon et al., 2002).

Using a diabetic rat model, we found that daily oral administration of 1 g of fruiting body of Cordyceps, about 4 g per kg of body weight, which is approximately one-fifth of the dose used by Kiho et al., significantly reduced the changes in fasting blood glucose (from d15 to d26), the serum concentrations of fructosamine (an index of short-term diabetic control (Johnson et al., 1983)), and the amount of water intake. These results imply that oral administration of the fruiting body of Cordyceps improved the control of blood glucose and attenuated the symptom of polydipsia in diabetic

animals. Due to the large amount of blood loss and the gavage stress caused by the OGTT on d26, we did not find a significant difference in the change in fasting blood glucose concentrations among the groups from d15 (i.e., the day of STZ injection) to d29, and in addition there was a general weight loss (6 to 9 grams in three days) and a decrease in food intake (2 to 4 grams per day) from d26 to d29. Therefore, we believe that the change in fasting blood glucose from d15 to d26 is more representative in reflecting the effect of Cordyceps on hyperglycemia than that from d15 to d29.

Moreover, the results of the OGTT demonstrated that the fruiting body, not carcass, of Cordyceps has hypoglycemic activity. For example, the significantly elevated blood glucose concentrations at 10, 20, 30, 60, 90 and 120 minutes of the OGTT in diabetic rats were lowered by the administration of the fruiting body. However, the concentrations of serum insulin were significantly elevated at 10, 20 and 30 minutes of the OGTT in normal rats not in diabetic rats, with or without Cordyceps. Even though we did not determine the insulin sensitivity of the cells, the unchanged insulin profile and improved glucose response during OGTT suggest that the fruiting body of Cordyceps may have improved glucose tolerance via increased insulin sensitivity (Carnevale Schianca et al., 2003). In consideration of the above, the hypoglycemic activity of the fruiting body of Cordyceps may be due to an improved glucose uptake and/or insulin resistance in cells.

It has been documented that a delay and/or reduction of carbohydrate absorption can be helpful in avoiding hyperglycemia in diabetic patients (Story et al., 1985). From the profile of post-loading curves in OGTT, we found that the STZ group had a peak of blood glucose concentration at 30 minutes and the CC, CF and FB groups had that peak at 60 minutes (Fig. 3). In addition, the blood glucose concentration from 10 to 120 minutes was significantly lower in the FB group than in the STZ group. Owing to the fact that the fiber content of Cordyceps is about 18.5%, we may presume that the anti-hyperglycemic activity of the fruiting body of Cordyceps is due to the fiber, so to account for the effects of high fiber content on glucose absorption, we fed the CON and STZ groups with cellulose and starch as the placebo. Therefore, we believe that not only the fiber but also the other components in the fruiting body of Cordyceps may improve the blood glucose control and glucose tolerance in diabetes. Furthermore, animals administered with a combined treatment of the fruiting body and carcass of Cordyceps may have diluted the components, thus resulting in the loss of the anti-hyperglycemic effects attributed by the fruiting body. The components of the fruiting body of Cordyceps which have anti-hyperglycemic activity need to be extracted and their mechanism need to be further investigated.

Recent evidence has indicated that the Cordyceps extracts have antitumor (Ohmori et al., 1989; Kuo et al., 1994; Yoshida et al., 1989), antiviral (Li et al., 1993), erythropoietic (Muller et al., 1991), anti-hyperlipidemic, anti-hypercholesterolemic (Kiho et al., 1996) and many other biological activities (Shiao et al., 1989; Wang et al., 1998). In the present study, we did not find any significant hematological changes in diabetic rats. Using this diabetic rat model, we could not show the hypolipidemic effect of Cordyceps. Their serum concentrations of triglyceride, cholesterol and free fatty acid were not significantly elevated before administrating the Cordyceps. However, we found that the weights of the thymuses were significantly increased in diabetic rats administered with the fruiting body of Cordyceps, and the weights of kidneys were significantly increased in those administered with the carcass of Cordyceps. Interestingly, the serum concentration of creatinine, an index of kidney function, paralleled the weight of the kidneys. The bioactivity of the carcass of Cordyceps on the kidney and the fruiting body of Cordyceps on the immune system requires further investigation.

Based on the results, we found that the Cordyceps administration influenced the diabetogenic effect of STZ and produced a milder diabetes. This result encouraged us to believe that orally administration of

Cordyceps may have potential benefit in preventing diabetes, since pancreatic damage induced by environmental chemicals and factors is a cause of diabetes. In summary, using a nicotinamide and streptozotocin-induced diabetic rat model, we demonstrated that the fruiting body of natural Cordyceps showed hypoglycemic activity via oral administration. We also believe that oral administration of natural Cordyceps with food is more applicable and acceptable for most people than intravenous or intraperitoneal injection of Cordyceps extract, as is used in most studies. Therefore, the fruiting body of Cordyceps may have potential use as a functional food in diabetic patients. However, its mechanism of action in improving glucose tolerance remains to be studied.

Acknowledgements

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