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**Original Article**

# Therapeutic Effects of Coptidis Rhizoma and Berberine in Streptozotocin-induced Diabetic Rats

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**Objectives:** We performed this study to compare the antidiabetic effects of Coptidis Rhizoma (CR) and its major component berberine with gliclazide.
**Materials and Methods**: Diabetic rats induced by injection of streptozotocin (STZ) 55mg/kg were treated with CR 100, 200, 400mg/kg and berberine 100mg/kg. After rats were treated for 5 days, serum glucose, total cholesterol, triglyceride, BUN, creatinine and antioxidant levels were determined.
**Results:** The cytotoxic effects of CR (0.1, 0.01, and 0.001mg/mL), berberine and gliclazide (0.1μM, 1μM, and 10μM) were tested in rat insulinoma (RIN) cells induced with 5mM STZ. The levels of fasting blood glucose, total cholesterol, triglyceride, BUN and creatinine of CR and berberine treated groups were reduced as much as that of gliclazide group in comparison to control groups, whereas total antioxidant levels increased. *In vitro* experiments showed that CR and berberine have a cytoprotective effect on RIN cells.

***Key Words*** : Coptidis rhizome; berberine; streptozotocin; gliclazide; diabetes.

## Introduction

Diabetes mellitus is a metabolic disorder of the endocrine system. The disease is found in all parts of the world and is rapidly increasing in most parts of the world[1)]. While there is much variation within the Asia-Pacific region, there is a rising prevalence of diabetes throughout the region. This is strongly associated with the lifestyle changes that follow large-scale industrialization, mechanization and urbanization. The current epidemic of diabetes is principally due to rises in Type 2 diabetes, although Type 1 diabetes prevalence rates are also increasing[2)].

According to its clinical manifestation, diabetes mellitus is categorized as *So-gal* or *So-dang* in traditional Korean medicine (TKM). From a TKM perspective, the cause of disease is classified into fluid consumption due to lung heat, excessive fire in the stomach, deficiency of kidney *yin*, deficiency of both *qi* and *yin,* and deficiency of both *yin* and *yang*. The treatment is based on the principle of eliminating heat by nourishing *yin*, moistening dryness and promoting fluid production[1)].

Coptidis Rhizoma (CR) is cited in *Dongeuibogam* ('Treasured Mirrors of Eastern Medicine') as a useful herbal medicine in the treatment of diabetes

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mellitus[3]. It has been reported that CR possesses hypocholesterolemic action[4] and antioxidant properties[5], which may play a important protective role against diabetes mellitus in the onset, complications and insulin resistance[6,7]. Also berberine, one of the main constituents of CR, is a type of isoquinoline alkaloid. It is suggested that berberine might be one of the principal antidiabetic constituents of CR. Berberine increases glucose uptake through a mechanism distinct from insulin, and activated adenosine monophosphate-activated protein kinase seems to be involved in the metabolic effect of berberine[8].

In this study, we treated rats with streptozotocin (STZ) and investigated the effects of CR and berberine on serum glucose, total cholesterol, triglyceride, BUN, creatinine, total antioxidant and cytotoxicity on RIN cells in comparison with gliclazide.

## Materials and Methods

### 1. Preparation of $H_2O$ Extracts from Coptidis Rhizoma (CR)

For extraction, 100g of CR was ground and extracted with boiling water for 4h. After centrifugation at 3000g for 20min, the supernatant was concentrated under reduced pressure to 100mL and freeze dried to 17.2g. The sterile extract was stored at -70℃.

### 2. Animal Preparation

Male Sprague-Dawley rats (200g) from Samtaco (Samtaco Co., Republic of Korea) were used. They were kept in a wire-bottomed cage under a conventional lighting regime with a dark condition. The room temperature (about 25℃) and humidity (about 60%) were controlled automatically. The rats were allowed access to laboratory pellet chow (Samyang Co., Republic of Korea) and water *ad libitum*. After 7 days of adaptation, STZ (Sigma Chemical Co, USA) dissolved in citrate buffer (pH 4.5) was injected intraperitoneally at a dose of 55 mg/kg following overnight fasting. Five days after injection, blood was taken from the tale vein. Rats with glucose levels above 180mg/dL were used as streptozotocin-induced diabetic rats. The animals were divided into 7 groups (n=5 per group), avoiding any intergroup differences in blood glucose levels. The control group received physiological saline (vehicle), while the other groups received the water extracted CR at a dose of 100, 200, or 400mg/kg, berberine (Sigma Chemical Co., USA) 100mg/kg, and gliclazide 40mg/kg body weight/day, respectively. After administration for 5 consecutive days, rats were killed by decapitation, blood samples were collected and serum was separated immediately by centrifugation.

### 3. Cell culture

The RIN cells were a generous gift from the Kyung Hee University Endocrinology Center, Republic of Korea. The cells was grown at 37℃ under a humidified, 5% $CO_2$ atmosphere in RPMI 1640 medium supplemented with 10% fetal bovine serum and 2nM glutamine, 10,000units/mL of penicillin, 50ug/mL of streptomycin, and 2.5ug/mL of amphotericin B. Cells from passages 5-9 were used.

### 4. Serum Analysis

1) Glucose assay

Glucose levels were measured using a commercial kit OneTouch Ultra (Inverness Medical Ltd., UK).

2) Total cholesterol assay

Total cholesterol levels were measured by using Enzymatic and colorimetry methods. ADVIA 1650 (Bayer, Japan) apparatus and cholesterol reagent (Bayer, Japan) were used.

3) Triglyceride assay

Triglyceride levels were measured using lipase, GK, GPD, and colorimetry methods. ADVIA 1650 (Bayer, Japan) apparatus and triglyceride reagent

(Bayer, USA) were used.

4) BUN assay

BUN levels were measured using the urease with GLDH method. ADVIA 1650 (Bayer, Japan) apparatus and urea nitrogen reagents (Bayer, USA) were used.

5) Creatinine assay

Creatinine levels were measured using the Jaffe method. ADVIA 1650 (Bayer, Japan) apparatus and creatine reagents (Bayer, USA) were used.

6) Total antioxidant assay

Total antioxidant levels were measured using the Total Antioxidant Status kit (RANDOX, USA) and calculated by the following equation:

$$\text{Factor} = \frac{\text{Concentration of standard}}{\Delta\text{A Bland} - \Delta\text{A Standard}}$$

A1: Mix well, incubate to bring to temperature and read initial absorbance.
A2: Mix and start timer simultaneously. Read absorbance after exactly 3 minutes.
A2-A1 = ⊿A of sample/standard/blank
mmol/L = Factor× (⊿A Blank-⊿A Sample)

### 5. MTT assay

An MTT assay was carried out to assess the cytotoxicity of STZ 5mM, CR 01, 10, and 100μg/mL, berberine and gliclazide $10^{-5}$, $10^{-6}$, $10^{-7}$M, respectively. Cells were placed in a 24-well plate Cell Counting Kit-8 (Dojindo, USA). After 48h of incubation at 37℃, MTT assay was performed according to the manufacturer's instructions and measured by an ELISA reader at 460 nm wavelength. The value was considered to reflect the activity of cell metabolism and the cytotoxicity index was calculated according to the following equation.

$$\text{C.I.}(\%) = \left(1 - \frac{\text{Sample O.D.}}{\text{Control O.D.}}\right) \times 100$$

### 6. Statistical Analysis

Data were presented as means ± S.D. Differences among the groups were analyzed by Student's t-test and those at $p < 0.05$ were considered significant.

## Results

### 1. Effect of Coptidis Rhizoma (CR) and berberine on fasting blood glucose levels

Fasting blood glucose levels were measured after rats were fasted for 12h on day 5. In the diabetic control group, the fasting blood glucose increased significantly. As with the gliclazide treatment, fasting blood glucose at every dose of CR and berberine decreased significantly (Fig. 1).

### 2. Effect of CR and berberine on lipid metabolic parameters, BUN and creatinine

The cholesterol levels decreased slightly but to a non-significant degree while triglyceride levels showed a statistically significant lowering effect. BUN and creatinine levels were effective at the doses of CR 100mg/kg and 200mg/kg. Overall effects were similar to that of gliclazide (Table 1).

### 3. Effect of CR and berberine on total antioxidant level

Total antioxidant levels generally increased on CR and berberine treatment, in CR 400mmol/L with a statistically significant increase while gliclazide had no such property (Table 1).

### 4. Prevention of STZ-induced cell death by CR

The RIN cells were cultured to near confluence. Using 5 mM STZ, RIN cells were treated with CR at doses of 1, 10, and 100 μg/mL and berberine, gliclazide at doses of 0.1μM, 1 μM, and 10 μM for 24 h, at which time the cells were harvested and their viability was analyzed. A single treatment of RIN cells with 5 mM STZ decreased the percentage

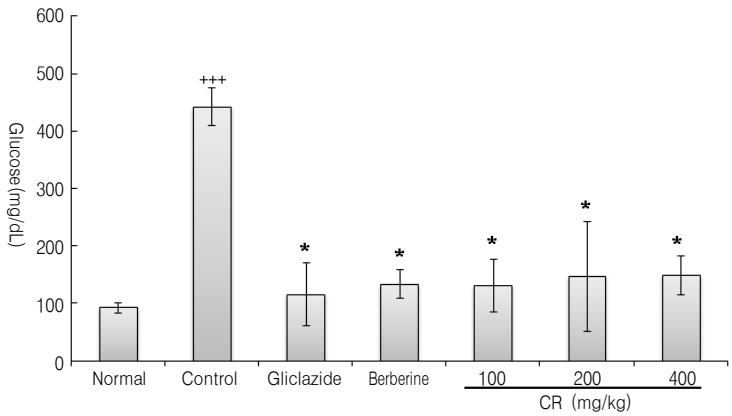


**Fig. 1.** Effect of CR, berberine and gliclazide on serum glucose level in streptozotocin-induced diabetic rats.
Data are represented as mean ± S.D. (n=5). +++ $p < 0.001$ compared with normal group, * $p < 0.001$ compared with the diabetic control group.

**Table 1.** Effect of CR and berberine on lipid metabolic parameters, BUN, creatinine and antioxidant

| Group | Dose (mg/kg) | Total Cholesterol (mg/dL) | Triglyceride (mg/dL) | BUN (mg/dL) | Creafinine (mg/dL) | Total Antioxidant |
|---|---|---|---|---|---|---|
| Normal | | 68.8±2.7 | 63.2±4.3 | 15.1±0.9 | 0.5±0.0 | 0.94±0.04 |
| Control | | 57.2±2.3$^{++}$ | 112.6±13.3$^{++}$ | 29.8±5.1$^{+++}$ | 0.7±0.1$^{+++}$ | 1.00±0.07 |
| Gliclazide | 40 | 47.4±1.2$^{**}$ | 28.0±6.9$^{*}$ | 14.6±3.0$^{*}$ | 0.4±0.0$^{**}$ | 0.99±0.05 |
| Berberine | 100 | 43.6±9.1 | 33.6±17.0$^{**}$ | 22.7±10.3 | 0.6±0.1 | 1.06±0.07 |
| | 100 | 66.6±4.7 | 57.8±18.9$^{*}$ | 16.6±1.6$^{**}$ | 0.6±0.0 | 1.13±0.10 |
| Coptis Rhizoma(CR) | 200 | 62.6±7.2 | 34.2±16.3$^{*}$ | 23.6±3.1 | 0.5±0.1$^{**}$ | 1003±0.02 |
| | 400 | 47.2±3.5 | 26.8±10.6$^{*}$ | 21.2±2.1 | 0.5±0.1 | 1.12±0.06$^{**}$ |

Data are represented as mean ± S.D. (n=5). +++$p < 0.001$ and ++$p < 0.05$ compared with normal group, *$p < 0.001$ and **$p < 0.05$ compared with the diabetic control group.

of live cells. Treatment of 5 mM STZ treated RIN cells along with CR, berberine and gliclazide, especially CR 10μg/mL, showed significantly increased cell viability (Fig. 2). On the other hand, berberine and gliclazide at higher concentration 10 μM, by itself, was cytotoxic to RIN cells (Fig. 3).

## Discussion

As in other countries that have undergone industrialization in recent years, the prevalence of diabetes has increased dramatically in Korea. While the prevalence of diabetes in Korean adults was estimated to be less than 0.5% in the 1960's, a recent study showed a dramatic increase to 7.2%[9].

Coptidis Rhizoma has traditionally been used in oriental medicine because it is said to drain fire and relieve toxicity, clear heat and drain dampness, clear heart fire, clear heat and stop bleeding, drain stomach fire and clear heat topically[10]. It also has been cited in *Dongeuibogam* as a useful herbal medicine in the treatment of diabetes mellitus[3].

Recent research on CR demonstrated inhibition of human esophageal cancer cell lines[11], potentiation of nerve growth in PC12 cells[12], and protective effects on pancreatic RINm5F cells[13] by a mechanism which

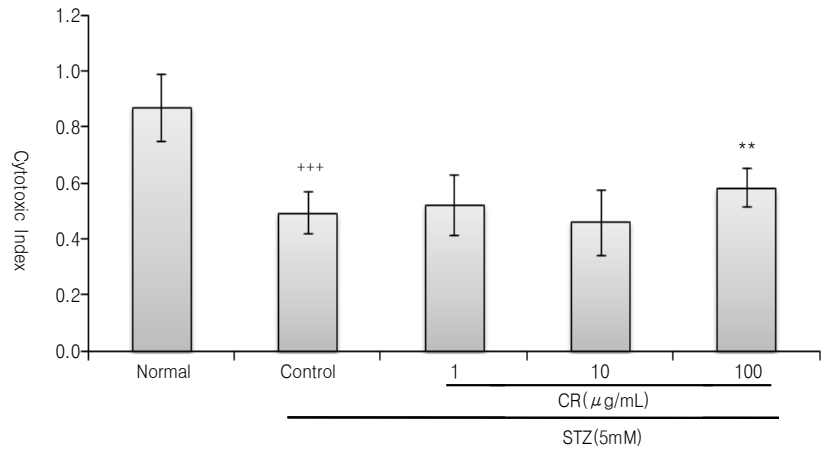


**Fig. 2.** Effect of CR on cytotoxicity assay. Cytotoxic index level in RIN cells treated with STZ 5 mM was reduced significantly.
Treatment of CR 100μg/mL had a significant cytoprotective effect against STZ 5 mM. Data are represented as mean ± S.D. (n=6). +++ $p<0.001$ compared with normal group, ** $p < 0.05$ compared with control group.

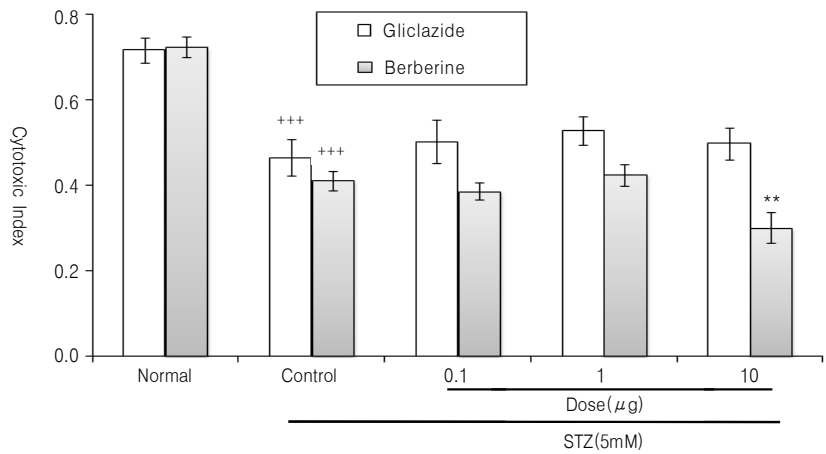


**Fig. 3.** Effect of berberine and gliclazide on cytotoxicity assay. Cytotoxic index level in RIN cells treated with STZ 5 mM was reduced significantly.
Treatment of berberine 10 uM produced RIN cell destruction which led to significant decrease. Data are represented as mean ± S.D. (n=6). +++ $p<0.001$ compared with normal control group, ** $p<0.05$ compared with control group.

involves the inhibition of NF-κβ activation[14]. Its major component berberine has been reported to inhibit arylamine N-acetyltransferase activity and gene expression in mouse leukemia L1210 cells[15], have an inhibitory effect on the mediastinal lymph node metastasis[16], inhibit cyclooxygenase-2 transcriptional activity in human colon cancer cells[17], have anti-inflammatory effects *in vitro* and *in vivo*[18] and inhibit the progression of diabetes induced by alloxan[19].

As diabetes mellitus is breaking out like a pandemic, much research about effective use of herbal medicine in its treatment is taking place all over the world[1,20,21]. We performed this study in order to compare the antidiabetic effect of CR and berberine in comparison with gliclazide.

In the present study CR and berberine showed a

clear antihyperglycemic effect, as much as that of gliclazide. In a previous study, berberine 1-10umol/L promoted insulin secretion in HIT-T15 cells incubated in the presence of glucose (0, 5, or 10mmol/L)[22], while in the present study CR did not show this insulin increasing effect (data not shown). This can be explained according to recent studies[23,24]. Berberine exerted a glucose-lowering effect in hepatocytes in an insulin-independent way[23]. As is well known, glucose is powerful in stimulating insulin release.

If blood glucose level is lowered through a hepatocyte metabolic pathway, in feedback the insulin release from pancreatic β-cell is reduced, as a result which counteracts' the insulin promoting action of berberine. Pan *et al*[24]. had another hypothesis. The fact that berberine has low bioavailability and shows poor absorption through the gut wall suggested that it may exert its antihyperglycemic effect in the intestinal tract before absorption and concluded that its effect is partly due to its ability to inhibit α-glucosidase and decrease glucose transport through the intestinal epithelium.

The typical secondary dyslipidemia of DM is characterized by increased concentration of total triglycerides (TG), very low density lipoproteins (VLDL) and decreased levels of high lipoprotein (HDL)[25]. Numerous studies have demonstrated that the risk and incidence of coronary heart disease (CHD) and vascular disease in patients with diabetes mellitus are higher than in non-diabetics. In fact, vascular disease accounts for more than 60% of the morbidity and mortality of diabetes[26]. CR is effective in reducing the pathological damage caused by hypercholesterolemia, through lowering serum cholesterol levels[27]. In addition, CR reduced the levels of liver cholesterol, but it did not reduce that of fecal cholesterol, suggesting that the cholesterol level-lowering effect resulted from the reduction of cholesterol synthesis, not the enhancement of its excretion. Our study did not show the same result as the research described above and a possible reason for this could be due to using a different rat feed.

The murine model induced by streptozotocin injection plus high fat chow feeding has been recognized as a type 2 diabetes models[22]. However, because patients with diabetes mellitus often have high blood lipid and cholesterol, the activity of CR blood vessel scavengers would contribute to the cure of diabetes mellitus.

Skeletal muscle contains large amounts of intracellular triglyceride (TG), which provides an important and readily available energy source with an overall caloric value exceeding that of glycogen stores. However, recent evidence suggests that if muscle contains abnormally high TG stores its sensitivity to insulin may be reduced[28]. An explanation for the delayed onset of insulin resistance may be that FFAs need to accumulate first as triglycerides inside muscle fiber. In support of this notion, several studies in animals and humans have demonstrated a close relationship between muscle fat content and insulin resistance[24,28,29]. The lowering triglyceride effects observed in CR and berberine were similar to that of gliclazide and also compatible with results of a previous study[4].

CR has a protective effect against the renal dysfunction caused by ischemia and the reperfusion process, and renal DNA of rats given CR extract orally showed a significantly lower DNA fragmentation rate[30]. Urea nitrogen, creatinine and free radicals affect renal tissue directly or secondarily, leading to a deterioration of renal function, and producing a vicious cycle which results in renal failure. Though the mechanism is not clear, our study and that of Cho *et al*[30]. suggest that CR and berberine can not only inhibit the production of uremic toxins but can also scavenge the reactive oxygen.

Histological analyses of the pancreases revealed that the β-cell mass was significantly larger in the diabetic mice treated with the antioxidant. As a possible cause, the antioxidant treatment suppressed apoptosis in β-cells without changing the rate of β-cell proliferation, supporting the hypothesis that in

chronic hyperglycemia, apoptosis induced by oxidative stress caused reduction of β-cell mass[31]. Hyperglycemia and characteristic dyslipidemia of DM along with increased oxidative stress leading to endothelial dysfunction have been implicated as early events in the pathogenesis of atherothrombotic macrovascular diseases[32]. Increased lipid peroxidation in tissues such as the liver and kidney implies that the tissues are susceptible to diabetic oxidative stress, leading to diabetic complications. Therefore, prevention of lipid peroxidation resulting from oxidative stress is considered to play a crucial role in protection against diabetes-induced disorders[33]. In general, oxidative injury occurs when endogenous antioxidant mechanism are unable to balance the rate of production of free radicals[34]. The result of our study compliments that of Kim *et al* [5]. showing that CR and berberine have effective anti-oxidative properties and could well scavenge excess free radicals with are not demonstrated in gliclazide.

In the present study, 5mM STZ caused destruction in RIN cells and was prevented only in CR. NO is an indispensable component of STZ-induced toxicity in RIN cells, and these findings indicate that the protective effect of CR against STZ-mediated killing is due to the inhibition of NO generation. Berberine in high doses was found to cause toxicity in RIN cells in our study. However, the hepatotoxicity or pancreotoxicity induced by berberine has never been observed clinically. Latha *et al* [35]. reported similar toxicity in high dose with *Scoparia dulcis*.

Our data suggest that CR and berberine have a beneficial effect in diabetic rats, which is exerted through its antihyperglycaemic, lipid modulation, and cytoprotective action with an extent of gliclazide also showing some properties that in gliclazide does not, like antioxidant properties.

Berberine and related isoquinoline alkaloids are quite different from sulfonylureas, biguanides and thiazolidinediones. Hence, berberine is a candidate agent in the treatment of diabetes. Thus, our study strongly supports the notion that supplementation of CR and berberine to diabetic patients would help in achieving good glycemic and metabolic control due to its antidiabetic effect.

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