

## Hypoglycemic Effect of Mushroom Fermented Milk in Streptozotocin-Induced Diabetic Rats

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Nutritional concentrations by chemical analyses of mushroom fermented milk were protein 2.87%, fat 0.09%, carbohydrates 6.0%, dietary fiber 0.3%, lactose 2.01%, sucrose 1.23%, calcium 95.9 mg/100 g and iron 0.08 mg/100 g. The present study was undertaken to investigate the hypoglycemic effects of the equal volume of either water (streptozotocin (STZ)-control rats), mushrooms water-extract (STZ-extract fed rats), mushroom fermented milk product (STZ-mushroom yogurt fed rats) or mushroom fermented milk supernatant (STZ-supernatant fed rats) (10%, v/w), in STZ-induced diabetic rats for 3 week period. The mushroom fermented milk given to the STZ-diabetic rats decreased the blood glucose significantly and increased the blood insulin, compared with the STZ-control rats. The supernatant and mushroom water extract also slightly retarded the development of hyperglycemia in the STZ-diabetic rats. Taken together the results, the mushroom yogurt may have a potential for the hypoglycemic effect in the STZ-diabetic rats.

**Key words** – mushroom fermented milk, hypoglycemic effect, streptozotocin, diabetes, pancreas

Resulted of many studies have been reported that various species of mushrooms show biological and physiological effects of wide ranges on lifestyle-related diseases, such as hypertension, hypercholesterolemia and cancer[10, 17,23]. Many species of mushrooms have also recently been reported to have hypoglycemic effects on diabetic model animals[15,27,30]. Some mushrooms, such as *Lentinus edodes* and *Ganoderma lucidum*, have been widely used for a long time in herbal mixtures of antidiabetic therapies and traditional antidiabetic medicines in Korea and other Asian area[6,27]. Polysaccharides in *Ganoderma lucidum* are one of the main hypoglycemic ingredients of hot water-extract from fruiting bodies of *Ganoderma lucidum*, which exhibited the hypoglycemic potential by increasing the plasma insulin levels in diabetic and normal animals[30,31]. The administration of edible mushrooms to animal models of insulin-dependent diabetes mellitus (IDDM) recovered the initial reductions in the plasma and pancreatic insulin concentrations and improved the hypoglycemic effect of exogenous insulin[4,20]. Recently, there has been increasing evidence that an aqueous extract of mushrooms affects the glucose metabolism of isolated murine abdominal muscle, insulin secretion by BRIN-BD11

cells and on the enhancement of insulin released by isolated islet of Langerhans cells in rats[1,2,4].

In many countries there is the wild spread belief that milk products fermented by lactic acid bacteria, such as yogurt, are beneficial toward hypertension, hypercholesterolemia, intestinal infections, and cancer[16,19,21,24,25]. However, their antidiabetic effects have hardly been studied to effects related with the lowering glycated hemoglobin (HbA1c), the improved glucose tolerance in neonatally streptozotocin (nSTZ)-induced diabetic rats fed a diet containing *Lactobacillus* GG cells[22] and the lowered glycemic and insulinemic indexes in healthy subjects fed fermented milk product[18]. The antidiabetic effects of edible mushrooms are chiefly found in the water-extracts of the fruiting bodies containing polysaccharides and glucan[8,28-31], but mushroom yogurt would be an ideal candidate for glycemic control. The relationship between mushroom yogurt and glycemic control has not been elucidated in diabetic animal models until now. Here, we reported, the firstly, evidence of the hypoglycemic effects after the oral administration of fermented mushroom milk product in STZ-diabetic rats.

## Materials and Methods

### Materials

The four strains of mushroom; *Lentinus edodes*, *Gano-*

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*derma lucidum*, *Pleurotus ostreatus* and *Flammulina velutipes*, used in this study were all cultivated in Korea, and obtained from local markets. The streptozotocin was purchased from Sigma Chemical Co, (St. Louis, MO, USA). The lactic acid bacteria used in the manufacture of the mushroom yogurt were *Lactobacillus acidophilus*, *Streptococcus thermophilus* and *Bifidobacterium longum*. All other chemicals and reagents were the best commercial grade available.

#### Preparation of fermented milk products

The lactic acid bacteria, *Lactobacillus acidophilus*, *Streptococcus thermophilus* and *Bifidobacterium longum*, were used as starters for the milk fermentation. The fermented milk product, referred to as "Biohub 100", was produced by using extract of these mushrooms, a lactic acid starter and skimmed milk powder, by Korean patent (KP 0378154) at the Biohub Co., Ltd, (Jinju, Korea). The safety of fermented mushroom milk "Biohub 100" has been granted (W-T sample ME 2002-037150 and Cust# 1352650) by the US Food and Drug Administration (FDA).

#### Chemical analyses of fermented mushroom milk

Dietary compositions in fermented mushroom milk were analyzed by according to the methods of AOAC INTERNATIONAL or accepted methods published in the literature at Woodson-Tenent Laboratories, Inc. (USA).

#### Diets and animal experiments

The five week old male Sprague-Dawley rats were purchased from Hyochang Science (Daegu, Korea) and housed individually in suspended wire-mesh stainless cages in a temperature controlled animal room (21~24°C), with a 12 hr light/dark cycle (07:00~19:00). The streptozotocin solution was prepared in 0.05 M citrate buffer (pH 4.5), immediately prior to injection into intraperitoneal with dosage of 50 mg/kg body weight following overnight fasting. Diabetes was defined as a blood glucose concentration above 300 mg/dl 48 hr after the STZ injection. The rats were divided into groups according to their treatment protocol. STZ-treatment rats were *ad libitum* with the same commercial powdered chow diet in which was incorporated an equal volume either water, mushroom yogurt, supernatant or water-extract and had free access to drinking water for 3 weeks. The body weights were recorded every week, and the water and food intake were recorded by every other day.

#### Analytical procedure

At the end of the treatment period, the animals were killed by withdrawing blood from the abdominal aorta, under light diethyl ether anesthesia, after an 8-hr fast. The pancreas were quickly removed and weighed, with the tissue weights onto the absolute (g) or relative weights (g/100 g body weight). The serum was separated by the centrifugation for determination of final glucose and insulin concentrations. The serum glucose and insulin concentrations were measured with a Fuji DRI-Chemiclinical Chemistry Analyzer (FUJI DRI-CHEM 3500, Tokyo, Japan) and an immunoradiometric assay kit (Biosource, Urope S.A., Nivelles, Belgium), respectively.

#### Oral glucose tolerance test (OGTT) in STZ-diabetic rats

The OGTT was performed in STZ-treatment rats fed the experimental diets after overnight fasting (water was allowed *ad libitum*). The blood glucose concentrations were measured by whole blood collected from the tail vein using a Lifescan glucose meter with One Touch test strips (Lifescan Inc., Milpitas, CA, USA), at 0, 30, 60, 90, 120 and 150 min after the oral administration of a glucose solution (one g/kg body weight).

#### Statistical analysis

The data resulted from experiments are presented as the means±SEM, and were analyzed by using a one way analysis of variance (ANOVA), with the differences analyzed using the Duncan's new multiple-range test[3]. A *p* value *p*<0.05 was accepted as being a statistically significant difference.

## Results and Discussion

#### Analyses of chemical components

The dietary compositions of fermented mushroom milk product are presented in Table 1 and 2. Concentrations of lactose and sucrose were 2.01 (wet weight) and 1.23 (wet weight), respectively. Glucose, fructose, and maltose concentrations were <0.02% (wet weight). In addition, concentrations of calcium, sodium and iron were 95.6, 67.3 and 0.08 mg/100 g, respectively.

#### Body weights, pancreatic weights, and water and food intake

The body weight gains, water and food intake, and

Table 1. Nutritional compositions and properties of fermented mushroom milk

|                            | Unit           | Concentrations |
|----------------------------|----------------|----------------|
| Carbohydrates, calculated  | %              | 6.00           |
| Dietary fiber              | %              | 0.30           |
| Ash                        | %              | 0.60           |
| Protein (N×6.25)           | %              | 2.87           |
| Total fat                  | %              | 0.09           |
| Saturated fatty acid       | %              | 0.06           |
| Monounsaturated fatty acid | %              | 0.02           |
| Polyunsaturated fatty acid | %              | <0.01          |
| Cholesterol                | mg/100 g       | 2.40           |
| Total energy               | calories/100 g | 36.1           |

Methods of AOAC INTERNATIONAL or accepted methods published in the literature were used to perform these analyses.

Table 2. Sugar and mineral compositions and properties of fermented mushroom milk

|          | Unit     | Concentrations |
|----------|----------|----------------|
| Sugars   | %        | 2.01           |
| Lactose  | %        | 1.23           |
| Sucrose  | %        | <0.02          |
| Glucose  | %        | <0.02          |
| Fructose | %        | <0.02          |
| Maltose  | %        | <0.02          |
| Minerals | mg/100 g | 95.9           |
| Calcium  | mg/100 g | 67.3           |
| Sodium   | mg/100 g | 0.08           |
| Iron     | mg/100 g | 0.08           |

Methods of AOAC INTERNATIONAL or accepted methods published in the literature were used to perform these analyses.

Table 3. Body weight gain, pancreatic weights, and water intake in the STZ-induced diabetic rats

| Ingredient                 | Normal                  | Streptozotocin-induced diabetic rats |                        |                         |                         |
|----------------------------|-------------------------|--------------------------------------|------------------------|-------------------------|-------------------------|
|                            |                         | Control                              | Mushroom yogurt        | Supernatant             | Extract                 |
| Body weight                |                         |                                      |                        |                         |                         |
| Initial (g)                | 140.0±4.0 <sup>ns</sup> | 143.3±3.1                            | 142.8±3.0              | 142.2±3.5               | 142.8±2.5               |
| Gain (g/3 weeks)           | 190.5±5.6 <sup>a</sup>  | 39.8±10.6 <sup>b</sup>               | 149.5±5.5 <sup>c</sup> | 91.2±8.2 <sup>d</sup>   | 72.0±12.1 <sup>d</sup>  |
| Water intake (ml/day)      | 48.3±3.6 <sup>a</sup>   | 180.4±5.9 <sup>b</sup>               | 38.8±1.1 <sup>a</sup>  | 160.0±11.2 <sup>b</sup> | 155.9±13.3 <sup>b</sup> |
| Food intake (g/rat/day)    | 24.3±1.6 <sup>na</sup>  | 26.5±2.2                             | 28.8±1.8               | 28.1±1.2                | 26.6±2.1                |
| Pancreas weight            |                         |                                      |                        |                         |                         |
| Absolute (g)               | 1.33±0.11 <sup>a</sup>  | 0.69±0.03 <sup>b</sup>               | 1.20±0.13 <sup>a</sup> | 0.77±0.09 <sup>b</sup>  | 0.79±0.04 <sup>b</sup>  |
| Relative (%) <sup>1)</sup> | 0.40±0.03 <sup>a</sup>  | 0.38±0.01 <sup>ab</sup>              | 0.41±0.04 <sup>a</sup> | 0.32±0.05 <sup>b</sup>  | 0.37±0.01 <sup>ab</sup> |

Rats were fed experimental diets containing mushroom fermented milk product, supernatant of mushroom fermented milk product or mushroom water-extract at the same volume (10.0%, v/w) for 3 weeks.

Values with different letters are significantly different at  $p < 0.05$ .

Values are means±SE of six rats per group.

Ns: not significant.

<sup>1)</sup>Relative (%) = g/100 g body weight.

absolute and related pancreatic weights are presented in Table 3. The body weight gain was significantly lower in the STZ-control rats compared with the normal rats, as expected[4,20]. However, the body weight reduction by STZ-treatment was markedly greater in the STZ-mushroom yogurt rats (3.76-fold), the STZ-supernatant (2.29-fold) and STZ-extract (1.81-fold) fed rats than rats of control group. The increase of body weight caused the administration of mushroom yogurt was consistent with previous reports, where the body weight gain was greater in neonatally STZ-diabetic rats fed a diet containing *Lactobacillus* GG cells, during a 9-wk experimental period, than in the normal rats [22]. The water intakes, as expected[4,20], were also significantly increased in the diabetic groups compared with the normal rats, exception for the rats fed the mushroom yogurt. However, the amounts of food consumed were almost the same within the experimental groups.

The absolute and relative pancreatic weights were significantly reduced in the diabetic rats compared to the normal rats, exception for the STZ-mushroom yogurt rats, but there were no differences in the pancreatic weights between the normal and STZ-mushroom yogurt fed rats. Furthermore, in our preliminary experiment, the pancreatic weights were remarkably increased, by 64.6%, in the STZ-mushroom yogurt fed rats compared with the STZ-diabetic rats bred long-term diet administration more than 4 months. Several investigators have reported that dietary components, such as mushroom lectin, raw soybean and polyenylphosphatidylcholine, resulted in a marked en-

largement of the pancreas treated with streptozotocin [7,13,14]. The reason for the pancreatic enlargement in the STZ-mushroom yogurt fed rats in the present study was unclear, but was probably, in part, caused by protection of the islet  $\beta$ -cells from the STZ-induced cytotoxic action, and the increase in the exocrine tissue and endocrine islet in the STZ-diabetic rats fed on mushrooms and other components[4,13,20,26]. Interestingly, lectin, a glycoprotein from mushrooms, has been shown to significantly increase the pancreatic weight (approximately 23%) in rats when given in large doses (25 mg/rat/day) for short periods, or low doses (2 mg/rat/day) for long periods (24 weeks)[7].

#### Blood glucose concentrations

The fasting blood glucose concentrations were significantly increased, 3.96-fold, in the STZ-control rats compared with the normal rats (Table 4). However, its concentration was dramatically decreased in the STZ-mushroom yogurt, STZ-supernatant and STZ-extract fed rats, by 75.3, 53.9 and 46.5%, respectively. However, the blood glucose concentrations in the mushroom treatment groups were markedly lower in the STZ-mushroom yogurt and STZ-supernatant fed rats than in the STZ-extract fed rats with the same administration volume. It was reported that the polysaccharides isolated from the fruiting body of *Ganoderma lucidum* exhibited the hypoglycemic potential by increasing the plasma insulin level or protecting against alloxan-induced pancreatic islets damage in normal mice and diabetic rats[30,31]. The polysaccharides of *Ganoderma lucidum* having hypoglycemic effect were extracted by hot water from the fruiting body. It consists of rhamnose, xylose, fructose, galactose, mannose, and glucose with molar ratios of 0.79: 0.96: 2.94: 0.17: 0.38: 7.94 and are linked together by beta-glycosidic linkages[30,31]. Previous studies have also shown that the fasting blood glucose concentrations in genetically diabetic mice and STZ-induced diabetic mice, fed on diet containing water-soluble poly-

saccharide from fruit bodies of mushroom (*Auricularia auricular* and *Tremella aurantia*), were significantly decreased [9,28]. In addition, other mushrooms have been reported to show hypoglycemic effects on diabetic rats or mice[5, 6,11,12,29]. Since mushroom fermented milk product was produced by using hot water extract which contains polysaccharides having antidiabetic activity from *Ganoderma lucidum* fruiting bodies, the hypoglycemic effect of fermented mushroom milk is reasonable.

#### Insulin concentrations

The blood insulin concentrations were significantly lowered, by 14.5%, in the STZ-diabetic rats compared with the normal rats (Table 4). In the STZ-diabetic groups, the blood insulin concentrations were markedly higher in the mushroom treatment groups than in the STZ-diabetic group. In particular, the STZ-mushroom yogurt fed rats (61.5%) were the most strongly effected, whereas the STZ-supernatant (13.3%) and STZ-extract fed rats (18.9%) were relatively lower effected. These results are reflected in the significant and positive correlation between the blood glucose and the blood insulin levels, and the absolute pancreatic weights, in this study.

It has also been reported that in nSTZ-diabetic rats, fed a diet supplemented with *Lactobacillus* GG cells, the serum insulin level 30 min after glucose loading was significantly higher than in the nSTZ-diabetic control rats[22]. In contrast, the hypoglycemic effect observed with the mushroom aqueous-extract possibly stimulated the glucose incorporation into glycogen (1.8-fold) in mouse abdominal muscles and enhanced the insulin secretion from the BRIN-BD11 pancreatic  $\beta$ -cell line and isolated islets of Langerhans in rats, in vitro[1,2,20]. The antihyperglycemic activity of *Agricus bisporus*, an edible mushroom, in STZ-diabetic mice also countered the initial reductions in the plasma and pancreatic insulin concentrations, suggesting that these effects may have been, in part, due to pro-

Table 4. Blood glucose and insulin concentrations in the STZ-induced diabetic rats

| Ingredient                   | Normal                        | Streptozotocin-induced diabetic rats |                              |                               |                               |
|------------------------------|-------------------------------|--------------------------------------|------------------------------|-------------------------------|-------------------------------|
|                              |                               | Control                              | Mushroom yogurt              | Supernatant                   | Extract                       |
| Blood glucose (mg/dl)        | 143.1 $\pm$ 12.4 <sup>a</sup> | 566.7 $\pm$ 9.6 <sup>b</sup>         | 139.7 $\pm$ 7.6 <sup>a</sup> | 261.3 $\pm$ 77.4 <sup>c</sup> | 303.0 $\pm$ 48.3 <sup>c</sup> |
| Blood insulin ( $\mu$ IU/ml) | 3.10 $\pm$ 0.40 <sup>a</sup>  | 2.65 $\pm$ 0.75 <sup>c</sup>         | 4.28 $\pm$ 0.77 <sup>b</sup> | 3.03 $\pm$ 0.43 <sup>a</sup>  | 3.15 $\pm$ 0.85 <sup>a</sup>  |

Rats were fed experimental diets containing mushroom fermented milk product, supernatant of mushroom fermented milk product or mushroom water-extract at the same volume (10.0%, v/w) for 3 weeks.

Values with different letters are significantly different at  $p < 0.05$ .

Values are means  $\pm$  SE of six rats per group.

tection of the  $\beta$ -cells by the cytotoxic action of STZ[4,20]. Previous studies have shown that digested mushrooms, or something in the extract, influence the glucose and/or insulin metabolisms, probably by enhancing the insulin sensitivity[12,15]. An exopolymer (200 mg/kg BW) produced from *Lentinus edodes* reduced both the plasma glucose and insulin levels by 22%[27]. These results suggested that the antihyperglycemic activity of mushroom may exert effects on the insulin-secretion and insulin-like action[4]. Consequently, the increase in the blood insulin concentration in diabetes mellitus caused by mushroom yogurt may be an important factor in improving the hyperglycemia of STZ-induced diabetes.

### OGTT in STZ-diabetic rats

Fig. 1 shows the results of the OGTT after treatment with the experimental diets, and are given as the percentage increase in the fasting blood glucose concentrations, as the basal blood glucose concentration among the experimental groups were dissimilar before the glucose loading. The blood glucose concentrations in the STZ-diabetic rats were significantly increased following the oral administration of glucose, and the treatment with the mushroom yogurt partially restored glucose tolerance. The peak increase in the blood glucose was observed after 30 min in all the experimental groups, exception for the STZ-mushroom yogurt fed rats, which was observed after the first hour. It has been reported that the nSTZ-diabetic

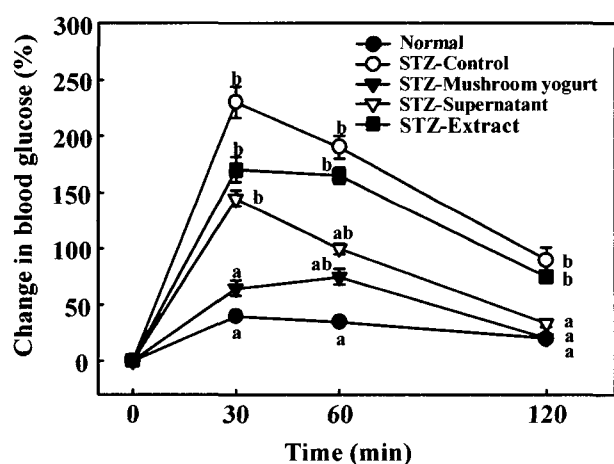


Fig. 1. Blood glucose response to the oral glucose tolerance test (OGTT) in the STZ-induced diabetic rats. The results are given as the percentage increase in the fasting blood glucose concentrations. Values with different letters are significantly different at  $p < 0.05$ . (mean  $\pm$  S.E.,  $n=6$ ).

rats fed diets containing *Lactobacillus* GG cells showed an improved glucose tolerance compared with nSTZ-diabetic control rats[22]. A previous study has also demonstrated that fermented milk products improve the blood glucose responses in healthy subjects fed yogurt, such as Filmjolk or Ropy milk[18]. Consequently, the stimulated insulin secretion due to mushroom yogurt feeding may be an important factor in improving the hyperglycemia and impaired glucose tolerance of diabetic rats. This assumption is supported by the facts that the concentration of post-prandial blood glucose was lower in the genetically diabetic KK-A<sup>y</sup> mice fed water-soluble polysaccharide of mushroom fruit bodies[28,29]. The improvement of the glucose tolerance by lactic acid bacteria has also been attributed to an enhanced activity of the  $\beta$ -cells of the pancreas, resulting in the secretion of a large amount of insulin 30 min after glucose solution administration[22]. Thus, these results indicated mushroom fermented milk containing both lactic acid bacteria and mushroom extract could improve glucose tolerance in the diabetic rats.

Thus, the present study has demonstrated for the first time that the administration of fermented mushroom milk products in the STZ-diabetic rats almost result in the prevention of the diabetogenic action of STZ, as reflected by the greater body weight gain, the lower blood glucose level and water intake, and the higher insulin level than normal rats. The intake of mushroom fermented milk products supernatant also tended to improve the glucose and insulin concentrations. Further investigations are needed to identify the mechanism of the antihyperglycemic effect of the extract in non-insulin-dependent (Type II) diabetes mellitus (NIDDM), as well as a dose-dependently administration study in insulin-dependent (Type I) diabetes mellitus (IDDM).

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**초록 : 당뇨병 흰쥐에서 버섯 추출물 함유 발효유 첨가 식이의 혈당강화작용**

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버섯 추출물을 첨가하여 유산 발효시킨 버섯발효유와 이때 사용된 버섯 추출물 및 버섯발효유 상등액의 항당뇨 효과를 규명하고자 Sprague-Dawley 수컷에 streptozotocin을 50 mg/kg body weight씩 복강내 주사하여 당뇨를 유발시켜 검토하였다. 버섯발효유, 상등액 및 버섯 추출물을 식이 중에 10% (v/w)씩 동량 첨가한 식이를 3주간 급여한 후 혈당치, 인슐린 농도 및 경구당부하실험을 실시하였다. 버섯발효유의 이화학적 성분을 분석한 결과 단백질 2.87%, 지방 0.09%, 탄수화물 6.0%, 식이섬유 0.3%, 락토스 2.01%, 슈크로스 1.23% 및 칼슘과 철 성분을 각각 95.9 및 0.08 mg/100 g 함유하고 있었다. Streptozotocin-유발 대조군 당뇨쥐에 비해 버섯발효유 투여군에서 현저한 혈당강화 효과가 있었으며, 이러한 효과는 인슐린 농도증가에 의한 것으로 나타났다. 또한, 버섯발효유 상등액 및 버섯 추출물에도 혈당강화 효과가 있는 것으로 나타났다. 실험 종료시점에 실시한 경구당부하실험에서도 버섯발효유, 상등액 및 추출물 순으로 현저한 효과를 보였다. 이상의 결과로 볼 때 혈당강화 효과가 있는 버섯과 유산균을 접목한 버섯발효유 제조는 이들 상호간의 시너지 효과에 의해 당뇨병 흰쥐에서 현저한 항당뇨 효과를 발휘하였다.