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In vivo Investigation of Anti-diabetic Properties of Ripe Onion Juice in Normal and Streptozotocin-induced Diabetic Rats

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ABSTRACT: The acute and subacute hypoglycemic and antihyperglycemic effects of drinkable ripe onion juice (Commercial product name is "Black Onion Extract") were investigated in normal and streptozotocin-induced diabetic rats. For tests of acute and subacute hypoglycemic effects, ripe onion juice (5 and 15 mL/kg b.w.) was administered by oral gavage to normal Sprague Dawley rats and measurements of fasting glucose levels and oral glucose tolerance tests were performed. Tolbutamide was used as a reference drug at a single oral dose of 250 mg/kg b.w. To test anti-hyperglycemic activity, the ripe onion juice was administered to streptozotocin-induced diabetic rats by oral gavage at single dose of 15 mL/kg b.w. per day for 7 consecutive days. Oral administration of the ripe onion juice at either dosed level of 5 or 15 mL/kg b.w. showed no remarkable acute hypoglycemic effect in normal rats. The two dosed levels caused a relatively small reduction, only 18% and 12% (5 and 15 mL/kg b.w., respectively) decrease in glucose levels at 2 h after glucose loading in normal rats. However, at 3 h after glucose loading, blood glucose levels in the ripe onion juice-dosed rats were decreased to the corresponding blood glucose level in tolbutamide-dosed rats. Although showing weak hypoglycemic potential compared to that of tolbutamide, oral administration of ripe onion juice (15 mL/kg b.w.) for a short period (8 days) resulted in a slight reduction in the blood glucose levels that had elevated in Streptozotocin-induced diabetic rats. In conclusion, these results suggest that the commercial product "Black Onion Extract" may possess anti-hyperglycemic potential in diabetes.

Keywords: anti-diabetic, Endoplasmic Reticulum stress, hypoglycemic effect, onion, streptozotocin

INTRODUCTION

Diabetes mellitus is a metabolic disorder affecting the metabolism of carbohydrate, fat and protein. The disease is classified as type 1 diabetes due to islet beta-cell destruction, type 2 diabetes with varying degree of insulin resistance and/or insulin secretion deficiency, gestational diabetes, and other specific types of diabetes (1). Type 2 diabetes mellitus is the most common form of diabetes, accounting for 90∼95% of all diabetic patients. Type 2 diabetes mellitus is a heterogeneous disorder characterized by a progressive decline in insulin action (insulin resistance), followed by the inability of β-cells to compensate for insulin resistance (β-cell dysfunction) (2). Controlling hyperglycemia, tight control of blood glucose levels and prevention of diabetic complications are the major goals in Type 2 diabetes treatment (1).

Recently there has been a growing interest in alternative therapies, including the use of plant foods, to treat diabetic patients (3). Onion (*Allium cepa* L.) is a bulbous herb belonging to the vegetable family Alliceae, and is a widely used food ingredient as well as a common spice all over the world. Onion is one of the richest sources of flavonoids and organosulfur compounds that possess strong antioxidant activities (4-6). Thus, onion intake is reported to have several beneficial effects on health, such as preventing tumors and cancers (7,8), cardiovascular diseases (9), hypertension (10), hypoglycemic and hypocholesterolemic effects (11,12) as well as improving diabetic status (12-14).

A number of studies have focused on the ability of onion to ameliorate diabetes, with many of them reporting both hypoglycemic and hypolipidemic effects in animal models of chemically induced non-insulin-dependent diabetes (12,15,16). However, the effects of ripe onion juice on hypoglycemic activity and on anti-diabetic activ-

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ity have not been evaluated. Hence, in the present study, we investigated the effect of ripe onion juice, commercially called "Black Onion Extract", on blood glucose levels in glucose-fed hyperglycemic, streptozotocin (STZ)-induced diabetic and normal rats compared to tolbutamide as a reference standard.

MATERIALS AND METHODS

Preparation of "Black Onion Exract"

In this study, we used a commercial product "Black Onion Extract", a drinkable ripe onion juice, manufactured by New Green Food Co., Ltd. (Changnyeung, Korea). According to the company, the "Black Onion Extract" was manufactured through the processing of ripening the onion for 16 days. Detailed ripening condition for 16 days was as follows: for first day at 0°C, for second day through fourth day at 78°C, for fifth day through seventh day at 45°C, for eighth day through tenth day at 60°C, for eleventh day through thirteenth day at 75°C, and for last three days at 50°C. During the ripening period, onion coats with the concentrated functional components were produced. By applying Steam Emission Extract method, ingredients of onion were concentrated to the "Black Onion Extract" and the residual unpleasant smell of onions was effectively eliminated.

Acute toxicity

The acute toxicity test was performed by administration of ripe onion juice using oral gastric gavages at doses of 5, 10, 15, 20 and 25 mL/kg b.w. to groups of 6 male Sprague-Dawley rats, and maintained for 14 days. General behavior of rats was recorded continuously for 12 h and daily for a further 2 weeks for any eventual mortality.

Determination of the blood glucose levels

Blood glucose concentrations were measured using automatic analysis (Accu-Chek Active Glucose, Roche Diagnostics, Mannheim, Germany).

Effect in normoglycemic animals

Fasting blood glucose level of each animal was determined at the beginning of the experiment, after overnight fasting with free access to water. The ripe onion juice (5 and 15 mL/kg b.w.) was single dosed using oral gastric gavages to test groups of animals. Tolbutamide (250 mg/kg b.w.) was single dosed using oral gastric gavages to the positive control group. Blood samples were collected from tail vein every 0.5 h for 4 h after the oral administration of test samples.

Oral glucose tolerance test (OGTT)

Fasting blood sugar level of each rat was determined at zero-time, after overnight fasting with free access to water. Glucose (5 g/kg b.w.) was orally administered 30 min after oral administration of the test samples or vehicle (for control). Blood glucose concentrations were measured just before and 0.5, 1, 1.5, 2, 3, and 4 h after the oral administration of the test samples.

Effects on streptozotocin-induced diabetic rats

Induction of diabetes: Diabetes was induced in male Sprague-Dawley rats (160~200 g) by the intraperitoneal injection of streptozotocin (STZ) at a single dose of 60 mg/kg b.w. dissolved in 0.1 M citrate buffer, pH 4.5. Two days after STZ injection, blood glucose levels were measured by using a glucometer (Johnson & Johnson, New Brunswick, NJ, USA) and the animals with blood glucose levels above 300 mg/dL were considered diabetic. Diabetic rats (blood glucose level ≥300 mg/dL) were subdivided into three groups (n=6 per group): group I received only natural food, group II orally received the Black Onion Extract (15 mL/kg b.w, single), and group III orally received tolbutamide (250 mg/kg b.w.).

Determination of hypoglycemic activity on acute administration: Test samples were given orally using oral gastric gavages to the overnight fasted animals. The blood glucose concentrations of the animals were measured at the beginning of the study and the measurements were repeated at 0.5, 1, 2, 4 and 6 h after the initiation of the experiment.

Determination of hypoglycemic activity on subacute administration: The ripe onion juice (15 mL/kg b.w.) was administered once a day for 7 consecutive days using oral gastric gavages. Blood glucose level of each animal was determined at 1st, 3rd, 5th and 8th days after the administration of the ripe onion juice. Body weight of animals was also monitored on these days.

Statistical analysis

Results are expressed as means±SEM for groups of six animals each, and differences between groups were tested for significance using two-way analysis of variance (ANOVA) followed by a *post-hoc* Duncan's multiple range test. The statistical analyses were performed on a Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Acute and subacute toxicity of ripe onion juice

Toxicity of ripe onion juice in Sprague-Dawley rats was tested using oral gastric gavages at doses of 5, 10, 15, 20 and 25 mL/kg b.w. for 14 days. No rats at all dose ranges were dead until the end of the study, indicating that the tolerated dose of ripe onion juice was above 25 mL/kg body weight. Ripe onion juice at all doses used in this

study did not show mortality or any remarkable symptoms of toxicity and/or any significant changes in general behavior in rats. The body weight gains of rats were not affected by the treatment. These results suggest that ripe onion juice has no acute and subacute toxic effects in Sprague-Dawley rats.

Acute hypoglycemic effect of ripe onion juice in normal rats

As a preliminary activity assessment, the ripe onion juice was administered to normal rats at two dose levels (5 and 15 mL/kg b.w.) to determine the acute effects on blood glucose concentrations. Changes in the blood glucose level of each group of animals were followed during a 4 h period. As shown in Table 1, the fasting blood glucose levels in the tested rats ranged between 59 and 66 mg/dL and no remarkable acute hypoglycemic effect of ripe onion juice was observed in normal rats. Administration of the ripe onion juice at both concentrations (5 and 15 mL/kg b.w.) in the fasted rats exhibited overall increase in their glucose levels through the duration of the experiment. At 0.5 h after the ripe onion juice (5 and 15 mL/kg b.w.) doses, glucose levels were transiently increased compared to that in the untreated control group, suggesting that no remarkable effect on hypoglycemic activity by the ripe onion juice. Tolbutamide (250 mg/kg b.w., single oral dose) in control rats did not exhibit any significant alteration (hypoglycemic effect) in these glucose levels either through the duration of the experiment.

Oral glucose tolerance test in normal rats dosed with ripe onion juice

Results of the glucose tolerance test performed on normal rats dosed with ripe onion juice (5 and 15 mL/kg b.w.) are shown in Table 2. At thirty minutes after feeding with glucose (5 g/kg b.w., oral), the blood glucose level increased to 185 (247%) and 157.8 (240%) mg/dL in normal control group and in the tolbutamide dosed group, respectively, representing as a hyperglycemic peak. Administration of ripe onion juice with 5 and 15 mL/kg b.w. at thirty minutes after feeding with glucose (5 g/kg b.w., oral) also increased the blood glucose level to

Table 1. Effects of a single oral dose of ripe onion juice and tolbutamide on blood glucose level in overnight fasted normal rats

Time (h)	Blood glucose (mg/dL)				
	Control	Onion juice (5 mL/kg b.w.)	Onion juice (15 mL/kg b.w.)	Tolbutamide (250 mg/kg b.w.)	*P*-value
Fasting (0)	63 ± 4^{b}	59 ± 1^{a}	66 ± 6^{a}	61 ± 3	NS
0.5	62 ± 3^{Ab}	101 ± 5^{Bd}	125 ± 12^{Ce}	61 ± 6^{A}	0.000***
1	73 ± 5^{Ac}	85 ± 4^{Bb}	101 ± 2^{Cd}	66 ± 6^{A}	0.000***
1.5	65 ± 5^{Ab}	83 ± 4^{Bb}	99 ± 7^{Cc}	68 ± 4^{A}	0.000***
2	66 ± 6^{Ab}	88 ± 7^{Bb}	97 ± 5^{Cc}	66 ± 2^{A}	0.000***
2.5	80 ± 8^{Bd}	84 ± 3^{Bb}	93 ± 4^{Cb}	63 ± 4^{A}	0.000***
3	68 ± 5^{Ab}	87 ± 5^{Bb}	84 ± 6^{Bb}	60 ± 4^{A}	0.000***
3.5	59 ± 3^{Aa}	90 ± 3^{Bc}	96 ± 3^{Bc}	67 ± 2^{A}	0.000***
4	64 ± 5^{Ab}	80 ± 8^{Bb}	90 ± 2^{Bb}	62 ± 4^{A}	0.000***
P-value	0.000***	0.000***	0.000***	NS	

Values are given in mean±SEM for groups of six animals each. Capital letters signify the results of post-analysis for groups in *post-hoc* Duncan's multiple range test and lower-case alphabets signify the results of post-analysis for time, respectively. ***$P<0.001$.

Table 2. Effects of a single oral dose of ripe onion juice and tolbutamide on blood glucose level in oral glucose (5 g/kg) tolerance test in Sprague-Dawley rats

Time (h)	Glucose tolerance test (mg/dL)				
	Control	Onion juice (5 mL/kg b.w.)	Onion juice (15 mL/kg b.w.)	Tolbutamide (250 mg/kg b.w.)	*P*-value
0	61.3 ± 2.7^{a}	61.2 ± 2.7^{a}	62.5 ± 2.7^{a}	59.8 ± 3.8^{a}	NS
0.5	60.5 ± 2.5^{Aa}	108.6 ± 4.5^{Bc}	137 ± 11.2^{Cc}	60.6 ± 6.5^{Aa}	0.000***
1[1)]	75.0 ± 3.0^{Ba}	85.0 ± 3.6^{Cb}	101.4 ± 2.2^{Db}	65.8 ± 5.8^{Aa}	0.000***
1.5	185 ± 11.5^{d}	181.4 ± 10.3^{e}	193 ± 16.8^{e}	157.8 ± 39.0^{b}	NS
2	158 ± 14.6^{c}	157.8 ± 14.6 $(13.0)^{d}$	174.4 ± 12.1 $(9.6)^{d}$	141.8 ± 40.6 $(10.2)^{b}$	NS
3	148 ± 6.3^{Ac}	149.2 ± 9.0 $(5.5)^{Bd}$	170.2 ± 19.0 $(2.4)^{Bd}$	115.2 ± 37.8 $(18.8)^{Ab}$	0.032*
4	122 ± 17.6^{b}	104.8 ± 9.3 $(34.2)^{c}$	115.8 ± 12.6 $(32.0)^{c}$	110 ± 27.2 $(4.5)^{b}$	NS
P-value	0.000***	0.000***	0.000***	0.000***	

[1)]Glucose (5 g/kg b.w.) loaded.

Values are given in mean±SEM for groups of six animals each. Values in parenthesis indicate the percentage lowering of blood glucose level in comparison to the previous time-point reading. Capital letters signify the results of post-analysis for groups in *post-hoc* Duncan's multiple range test and lower-case alphabets signify the results of post-analysis for time, respectively. *$P<0.05$, ***$P<0.001$.

181.4 (213%) and 193 (190%) mg/dL, respectively. Nevertheless, after these substantial increases in glucose levels, the ripe onion juice administration significantly reduced the blood glucose levels to a level below that produced in the control group after three hours. Single oral dosage of tolbutamide (250 mg/kg b.w.) caused a significant reduction (27%) in glucose levels at 2 h after its administration, while for the same period of time after glucose loading administration, the groups of ripe onion juice (5 and 15 mL/kg) showed a relatively slight reduction, i.e., 18% and 12 % decrease in glucose levels, respectively. At 3 h after glucose load, blood glucose levels in the ripe onion juice-administered groups approached the level of tolbutamide-dosed group; this showed that the decrease (42.2%) in blood glucose levels at 3 h after glucose load was most efficient in the 5 mL/kg ripe onion juice-administered groups, which was lower than the decrease (30.3%) level in the tolbutamide-dosed group. Particularly, compared to the ripe onion juice treated groups, the control rat group showed no remarkable decrease in glucose level even at 3 h after glucose load.

Hypoglycemic effects of ripe onion juice on streptozotocin-induced diabetic rats

As a preliminary activity assessment, ripe onion juice (15 mL/kg b.w.) was administered to STZ-induced diabetic rats to determine the acute effect on blood glucose concentrations under the diabetic condition. Changes in the blood glucose level in each group of rats were followed during a 6 h period. Administration of STZ (60 mg/kg/i.p.) led to over a six-fold elevation in blood glucose levels compared to normal rats, which were maintained over a period of 3 weeks (Table 3). The oral administration of tolbutamide (250 mg/kg b.w.) showed a significant reduction in glucose level throughout the experimental period, especially at 0.5, 1 and 2 h after its administration. The administration of tolbutamide produced a significant reduction in glucose level by 39 mg/dL after 6 h, while for the same period of time, only a slight decrease in blood glucose level compared to control was observed after the administration of ripe onion juice; however, the decrease was much comparable to that of the tolbutamide administrated group. The administration of ripe onion juice (15 mL/kg b.w.) also produced a reduction in glucose level by 18 mg/dL after 6 h, which is lower than the level decreased by tolbutamide administration.

To determine possible subacute hypoglycemic effects of ripe onion juice and tolbutamide, first, a single intraperitoneal administration of STZ into diabetic rats (60 mg/kg) led to over a five-fold elevation of blood glucose levels, which were maintained over a period of eight days (Table 4). Orally administered tolbutamide showed

Table 3. Effects of ripe onion juice and tolbutamide on blood glucose level in STZ-induced diabetic rats

Time (h)	Mean blood glucose concentration±SEM (mg/dL)			
	Control (STZ-injected)	Onion juice (15 mL/kg b.w.)	Tolbutamide (250 mg/kg b.w.)	*P*-value
0	323 ± 7^{b}	326 ± 5^{b}	323 ± 8^{b}	NS
0.5	373 ± 9^{Bb}	358 ± 11^{Bb}	325 ± 21^{Ab}	0.004**
1	340 ± 17^{b}	332 ± 11^{b}	308 ± 22^{a}	NS
2	333 ± 13^{Bb}	329 ± 13^{Bb}	301 ± 17^{Aa}	0.045*
4	311 ± 14^{a}	309 ± 7^{a}	310 ± 10^{a}	NS
6	311 ± 8^{Ba}	308 ± 10^{Ba}	284 ± 10^{Aa}	0.001**
P-value	0.000***	0.000***	0.025*	

Diabetes induction in male Sprague-Dawley rats was performed by the intraperitoneal injection of streptozotocin (STZ) at a single dose of 60 mg/kg body weight.
Tolbutamide (250 mg/kg b.w.) or Onion Juice (15 mL/kg b.w.) was orally dosed in STZ-induced diabetic rats, respectively. Capital letters signify the results of post-analysis for groups in *post-hoc* Duncan's multiple range testand lower-case alphabets signify the results of post-analysis for time, respectively. *P<0.05, **P<0.01, ***P<0.001.

Table 4. Subacute hypoglycemic effects of ripe onion juice and tolbutamide on STZ-induced-diabetic rats

Treatment	Mean blood glucose concentration±SEM (mg/dL)			
	1st day	3rd day	5th day	8th day
Control (Untreated)	61.3±1.5	61.2±1.2	62.5±1.1	61.8±1.3
STZ treated	357±17	405±19 (-13)	368±17 (-3)	338±13 (6)
Tolbutamide (250 mg/kg)	363±8	325±21 (11)	308±22 (16)	276±17 (24)
Onion Juice (15 mL/kg)	366±5	378±11 (-3)	332±16 (9)	315±8 (14)

Values are given in mean±SEM for groups of six animals each. Values in parenthesis indicate the percentage lowering of blood sugar level in comparison to the reading at 1st day.
Tolbutamide (250 mg/kg/day, single) or Onion Juice (15 mL/kg/day for 7 consecutive days) was orally dosed in STZ-induced diabetic rats, respectively.

a tendency of reduction (24%) in plasma glucose levels after eight days. Although showing weak hypoglycemic effect compared to that of tolbutamide, a single dose of ripe onion juice (15 mL/kg) also reduced blood glucose in STZ-induced diabetic rats after its oral administration daily for eight days.

DISCUSSION

The objective of this study was to investigate whether the commercial product "Black Onion Extract", a drinkable ripe onion juice, could produce hypoglycemic activity in normal rats and antihyperglycemic effect in streptozotocin-induced diabetic rats. The results from this study first indicate a potential use of onion (*Allium cepa*) as a beneficial anti-hyperglycemic food supplement in diabetes. Considerable numbers of studies have been reported about the antidiabetic effects of various forms of onions, including aqueous onion extracts (15,16), dietary onions (12,17) and isolated or synthesized active compounds in onions (13,14,18). All of these studies reported significant antihyperglycemic effects of onions and its compounds in alloxan- or STZ-induced diabetic rats. In the present study, we found that, although low/weak hypoglycemic activity exhibited in normal rats, the commercial products of onions, drinkable ripe onion juice, possess antidiabetic potential in STZ-induced Sprague-Dawley rats. STZ is widely used for induction of experimental diabetes mellitus because of its toxic effect to pancreatic β-cells, which are responsible for the secretion of insulin (19). Thus STZ-induced diabetes is characterized by uniform hyperglycemia. A clinically used tolbutamide (a sulphonylurea drug) is known to lower the blood glucose level by stimulating β-cells to release insulin (20). Since STZ induces diabetes by destroying β-cells and by impairing renal function (21), in the present study, tolbutamide exhibited mild hypoglycemic activity in the STZ diabetic rats.

In many clinical studies the hypoglycemic activity of *Allium cepa* has been demonstrated by showing that the addition of raw onion to the diet for non-insulin-dependent diabetic subjects decreased the dose of antidiabetic medication required to control the disease (22). Moreover, the oral administration of *Allium cepa* crude hydroalcoholic extract in alloxan-induced diabetic rats produced a significant hypoglycemic activity and favorable good health effects, which may be most probably attributed to improvement and/or regeneration of pancreatic β-cells (23). Some articles report that *Allium cepa* acts as a hypoglycemic agent by directly acting on tissues such as the liver and muscles, and altering the activities of the regulatory enzymes of glycolysis, gluconeogensesis, and other pathways, such as attenuation of ER stress, rather than increasing insulin levels and creating extra pancreatic effects (22,24,25). Recently, ER stress has been suggested to play a central role in the development of insulin resistance and diabetes by impairing insulin signaling (26-28); hence, effects of onion extracts or its components could possess the properties as potent antidiabetic agents by alleviate ER stress and should be explored.

Our results showed low hypoglycemic activity of ripe onion juice at two dose levels (5 and 15 mL/kg b.w.) in the normal male Sprague-Dawley rats. A possible explanation is due to the short period of the experiment. Thus, further long term studies for the hypoglycemic activity of ripe onion juice are required. Another possible explanation for this result is that some ingredients, in particular, volatile sulfur compounds including thiosulfonates and polysulfides for hypoglycemic activity might be loss during the product processing of ripe onion juice or by passing over its best distribution period. In fact, most of the sulfur compounds present in onions are in the form of cysteine derivatives, which are degraded during extraction by the enzyme allinase into a variety of volatile compounds including thiosulfonates and polysulfides (15). Kumari and Augusti (14) reported that S-methylcysteine sulfoxide isolated from onion has antihyperglycemic effect. Our observed increase in fasting blood glucose levels in the ripe onion juice-administered groups during the first 30 min after its oral dose is thought to be attributed to the glucogenic effects of *Allium cepa*, which might be from the cysteine present in onion (18). These glucogenic effects can counteract the common side effect (hypoglycemia) of antidiabetic agents currently used if *Allium cepa* is taken concurrently as a food supplement.

Excessive consumption of high doses of onion can lead to adverse effects on health, such as anemia, weight loss, and toxicity to the heart, liver, and kidneys. One study showed that high doses (500 mg/kg) given orally caused lung and tissue damage in rats (29). Oral dosage (5 and 15 mL/kg b.w.) of the ripe onion juice used in this study corresponds to 2 and 6 mg/kg b.w. by calculation, respectively, which are much lower contents from the concentration showing the toxic effect.

Our results show that the dose of ripe onion juice has antihyperglycemic activity is in agreement with reports previously published. Therefore, although detailed mechanisms of action have remained for further investigation, we proposed that taking ripe onion juice may prevent hyperglycemia in diabetic rats. In conclusion, the present study suggests that ripe onion juice may be able to normalize the blood glucose levels when doses are continuous for long periods. Although this paper is the only one reporting a drinkable commercial onion product containing antidiabetic potential, these findings provide

a basis for the use of this drinkable onion product for the prevention of diabetic patients. Thus, we suggest that usage of this product could be beneficial in prevention of type 2 diabetes mellitus. Of course, further studies for its long term effect for the prevention of diabetes are required.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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