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

Chul-Won Lee¹, Hyung-Seok Lee², Yong-Jun Cha³, Woo-Hong Joo⁴, Dae-Ook Kang⁵, and Ja-Young Moon⁵

¹Institute of Marine BioTechnology, Pusan National University, Busan 609-735, Korea
²KT&G Central Research Institute, Daejeon 305-805, Korea
³Department of Food and Nutrition, ⁴Department of Biology, ⁵Department of Biochemistry and Health Sciences, Changwon National University, Gyeongnam 641-773, Korea

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 Alliaceae, 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-
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 Extract”
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 (OGT)
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, 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.

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) | Control (5 mL/kg b.w.) | 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^ca | 61±6^a | 0.000*** |
| 1 | 73±5^ac | 85±4^bf | 101±2^ad | 66±6^a | 0.000*** |
| 1.5 | 65±5^ab | 83±4^bf | 99±7^c | 68±4^a | 0.000*** |
| 2 | 66±6^a | 88±7^b | 97±5^c | 66±2^a | 0.000*** |
| 2.5 | 80±6^bd | 84±3^bf | 93±4^d | 63±4^a | 0.000*** |
| 3 | 68±5^ab | 87±5^bf | 84±6^b | 60±4 | 0.000*** |
| 3.5 | 59±3^ab | 90±3^bc | 96±5^e | 67±2^a | 0.000*** |
| 4 | 64±5^ab | 80±1^ab | 90±2^b | 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) | Control (5 mL/kg b.w.) | 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^b | NS |
| 0.5 | 60.5±2.5^ab | 108.6±4.5^bc | 137±11.2^cd | 60.6±6.5^b | 0.000*** |
| 1 | 75.0±3.0^ab | 85.0±3.6^cb | 101±2.3^ab | 65.8±5.8^a | 0.000*** |
| 1.5 | 185±11.5^d | 181±10.3^c | 193±16.8^b | 157.8±39.0^a | NS |
| 2 | 158±14.6^c | 157±14.6 (13.0)^e | 174±12.1 (9.6)^f | 141±40.6 (10.2)^b | NS |
| 3 | 148±6.3^c | 149±9.0 (5.5)^f | 170±19.0 (2.4)^g | 115±37.8 (18.8)^ab | 0.032* |
| 4 | 122±17.6^b | 104±9.3 (34.2)^f | 115±12.6 (32.0)^c | 110±72.7 (4.5)^b | NS |
| P-value | 0.000*** | 0.000*** | 0.000*** | NS | |

^1Glucose (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.
Table 3. Effects of ripe onion juice and tolbutamide on blood glucose level in STZ-induced diabetic rats

| Time (h) | Control (STZ-injected) | Onion juice (15 mL/kg b.w.) | Tolbutamide (250 mg/kg b.w.) | P-value |
|---------|------------------------|----------------------------|----------------------------|---------|
| 0       | 323±7b                 | 326±5b                    | 323±8b                    | NS      |
| 0.5     | 373±10b                | 358±811b                  | 325±211b                  | 0.004** |
| 1       | 340±17b                | 332±11b                  | 308±224                  | NS      |
| 2       | 333±13b                | 329±13b                  | 304±174                  | 0.045*  |
| 4       | 311±24b                | 309±74b                  | 310±109                  | NS      |
| 6       | 311±10b                | 308±10b                 | 284±10b                  | 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 test and 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 | 1st day | 3rd day | 5th day | 8th day |
|-----------|---------|---------|---------|---------|
| Control (Untreated) | 61±1.5 | 61.2±1.2 | 62.5±1.1 | 61.8±1.3 |
| STZ treated | 357±17 | 405±19 (-13) | 366±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±18 (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.
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, gluconeogenesis, 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.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government MEST, Basic Research Promotion Fund (NRF-2009-013-C00041). This research was also financially supported by Changwon National University in 2011. We thank Mr. Jong-Soo Kyung, KT&G Central Research Institute for his technical support. We also thank Dr. Kwang-Hyun Cho, Changwon National University for his support of Statistical Analysis.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

REFERENCES

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. 1997. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 20: 1183-1197.
2. DeFronzo RA. 1997. Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes genes. Diabetes Rev 5: 177-269.
3. Srinivasan K. 2005. Plant foods in the management of diabetes mellitus: spices as beneficial antidiabetic food adjuncts. Int J Food Sci Nutr 56: 399-414.
4. Virtanen AL, Matikka K, Euj. 1976. The isolation of S-methyl-L-cysteine sulfoxide and S-n-propyl-L-cysteine sulfoxide from onion (Allium cepa) and the antibiotic activity of crushed onion. Acta Chem Scand 13: 1898-1900.
5. Block E. 1985. The chemistry of garlic and onions. Sci Am 252: 94-99.
6. Patil BS, Pika LM. 1995. Distribution of quercetin contents in different rings various coloured onion (Allium cepa L.) cultivars. J Hort Sci 70: 643-650.
7. Galeone C, Pelucchi C, Levi F, Negri E, Franceschi S, Talamini R, Giacosa A, La Vecchia C. 2006. Onion and garlic use and human cancer. Am J Clin Nutr 84: 1027-1032.
8. Belsman S. 1983. Onion and garlic oils inhibit tumor promotion. Carcinogenesis 4: 1063-1065.
9. Mennen LI, Sapincho D, de Bree A, Arnault N, Bertrais S, Galan P, Hercberg S. 2004. Consumption of foods rich in flavonoids is related to a decreased cardiovascular risk in apparently healthy French women. J Nutr 134: 923-926.
10. Sakai Y, Murakami T, Yamamoto Y. 2003. Antihypertensive effects of onion on NO synthase inhibitor-induced hypertensive rats and spontaneously hypertensive rats. Biosci Biotechnol Biochem 67: 1305-1311.
11. Kumari K, Augusti KT. 2007. Lipid lowering effect of S-methyl cysteine sulfoxide from Allium cepa Linn in high cholesterol diet fed rats. J Ethnopharmacol 109: 367-371.
12. Babu PS, Srinivasan K. 1997. Influence of dietary capsaicin and onion on the metabolic abnormalities associated with streptozotocin induced diabetes mellitus. Mol Cell Biochem 175: 49-57.
13. Kumari K, Mathew BC, Augusti KT. 1995. Antidiabetic and hypolipidemic effects of S-methyl cysteine sulfoxide isolated from Allium cepa Linn. Indian J Biochem Biophys 32: 49-54.
14. Kumari K, Augusti KT. 2002. Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (Allium cepa Linn) as compared to standard drugs in alloxan diabetic rats. Indian J Exp Biol 40: 1005-1009.
15. El-Demerdash FM, Yousef MI, El-Naga NL. 2005. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food Chem Toxicol 43: 57-63.
16. Campos KE, Diniz YS, Cataneo AC, Faine LA, Alves MJ, Novelli EL. 2003. Hypoglycemic and antioxidant effects of onion, Allium cepa: dietary onion addition, antioxidant activity and hypoglycemic effects on diabetic rats. Int J Food Sci Nutr 54: 241-246.
17. Jelodar GA, Maleki M, Motadayen MH, Sirus S. 2005. Effect of fenugreek, onion and garlic on blood glucose and histopathology of pancreas of alloxan-induced diabetic rats. Indian J Med Sci 59: 64-69.
18. Sheela CG, Kumud K, Augusti KT. 1995. Anti-diabetic effects of onion and garlic sulfoxide amino acids in rats. Planta Med 61: 356-357.
19. Like AA, Rossini AA. 1976. Streptozotocin-induced pancreatic insufficiencies: new model of diabetes mellitus. Science 193: 415-417.
20. Jafari MA, Aslam M, Javad K, Singh S. 2000. Effect of Punica granatum L. (flowers) on blood glucose level in normal and alloxan induced diabetic rats. J Ethnopharmacol 70: 309-314.
21. Gilman AG, Rall TW, Nies AS, Tayer P. 1990. Goodman and Gilman’s the pharmacological basis of therapeutics. 8th ed. Pergamon Press, New York, NY, USA. p 1317-1322.
22. Bhushan S. 1984. Effect of oral administration of raw onion on glucose tolerance test of diabetics: a comparison with tolbutamide. Curr Med Pract 28: 712-715.
23. Eldin IMT, Ahmed EM, Abdl Elwahab HM. 2009. Hypoglycemic activity and regeneration of pancreatic beta-cells produced by Allium cepa in alloxan-induced diabetic rats. Oman Journal of Pharmaceutical 1: 562-568.
24. Taj Eldin IM, Ahmed EM, Elwahab MHA. 2010. Preliminary study of the clinical hypoglycemic effects of Allium cepa (red onion) in type 1 and type 2 diabetic patients. Environ Health Insights 4: 71-77.
25. Yeo J, Kang YM, Cho, SI, Jung MH. 2011. Effects of a multi-herbal extract on type 2 diabetes. Chin Med 6: 10.
26. Fonseca SG, Burcin M, Gromada J, Urano F. 2009. Endoplasmic reticulum stress in beta-cells and development of diabetes. Curr Opin Pharmacol 9: 763-770.
27. Araki E, Oyadomari S, Mori M. 2003. Impact of endoplasmic reticulum stress pathway on pancreatic β-cells and diabetes mellitus. Exp Biol Med 228: 1213-1217.
28. Kaufman RJ, Back SH, Song B, Han J, Hassler J. 2010. The unfolded protein response is required to maintain the integrity of the endoplasmic reticulum, prevent oxidative stress and preserve differentiation in β-cells. Diabetes Obes Metab 1: 99-107.
29. Ali M, Thomson M, Afzal M. 2000. Garlic and onions: their effect on eicosanoid metabolism and its clinical relevance. Prostaglandins Leukot Essent Fatty Acids 62: 55-73.