College of Biotechnology and Food Engineering[1], Hefei University of Technology, Hefei; School of Biosystems Engineering and Food Science[2], Zhejiang University, Zhejiang, China

Hypoglycemic and hypolipidemic effects of a triterpenoid-rich extract from *Euryale* shell on streptozotocin-induced diabetic mice

Huaibo Yuan[1,2], Zhaobin Gong[1], Shaohua Meng[1], Guoqing He[2]

Received August 8, 2012, accepted September 7, 2012

Prof. Huaibo Yuan, College of Biotechnology and Food Engineering, Hefei University of Technology, Tunxi Road No.193, 230009 Hefei, China
yuanhuaibo001@163.com

Pharmazie 68: 227–231 (2013) *doi: 10.1691/ph.2013.2734*

The hypoglycemic and hypolipidemic effects of a triterpenoid-rich extract from the *Euryale* shell (ES) was analyzed in streptozotocin-induced diabetic mice. Normal and diabetic mice treated with glimepiride were used as negative and positive controls, respectively. Body weight, organ weight index and cholesterol-related lipid profile parameters were observed after 4 weeks. The hypoglycemic activity was assessed by fasting blood glucose (FBG) and fasting insulin (FINS) to calculate the insulin sensitivity index (ISI). In addition, the potentially regulative mechanisms on insulin resistance were discussed. The results indicated that a triterpenoid-rich extract of ES could inhibit reduction in the body weight of diabetic mice and regulate glucose metabolism. The hypolipidemic action after this extract supplementation was confirmed by significant ($p < 0.05$) decreases in the levels of cholesterol, LDL and triglycerides and increase in HDL compared with the untreated diabetic mice, especially when using a high dose, which suggested that the ES extract could effectively reverse the abnormal enlargement of the liver and spleen ($p < 0.01$). The present data suggest that the triterpenoid-rich extract from the ES has both hypoglycemic and hypolipidemic effects that can not only help cure and manage diabetes but also improve insulin resistance (IR).

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common endocrine disorder (King et al. 1998). It is a group of metabolic alterations characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (Bhavna Sharma et al. 2008). More than 150 million people suffer from TD2 M worldwide, and this number is likely to increase to 300 million by the year 2025 (Anusha Bhaskar et al. 2008). Chronic hyperglycemia in diabetes has been associated with the long-term damage, dysfunction and eventual failure of organs, especially the eyes, kidneys, nerves, heart and blood vessels (Huang et al. 2005). Additionally, either the availability of many anti-diabetes agents and pharmacotherapies targeting T2DM causes a great burden to patients, society, health care systems and the economy or their side effects and contraindications limit their use (Tahrani et al. 2010).

Medicinal plants provide a useful source of oral hypoglycemic compounds for the development of new pharmaceutical leads and as dietary supplements to existing therapies (Bailey and Day 1989). Current evidence has suggested that some plants, especially soluble supplements, result in some improvements in glucose metabolism (Brennan et al. 2005; Oliveira et al. 2005; Topping 2007). Some of the plants that are being used for the treatment of diabetes have received scientific or medicinal scrutiny, and even the WHO expert committee on diabetes recommends that this area warrants further attention. Consequently, plants have been used as sources of drugs for the treatment of diabetes in developing countries where the cost of conventional medicines is a burden to the population (Kim et al. 2009; Wood 2007; Yasuda et al. 2003).

Euryale ferox is a mature seed of the *Euryale* genus of Nymphaeaceae (Nath BK et al. 1985). Originally produced in Southeast Asia, and China, it has been cultivated for a long time. The outer package of the *Euryale ferox* seeds is a hard shell. In the processing of the *Euryale ferox*, many of the shells are discarded (Row et al. 2007). It has been used to treat kidney diseases (Zhao et al. 1994), and the anti-hyperglycemic activity of *Euryale ferox* seeds has been well established (Lee et al. 2002). However, there is little information on the effect of the extract from *Euryale* shell in diabetes and its role in improving lipid profiles.

The aim of this present work was to explore the scientific basis of the utility of the triterpenoid-rich extract from ES on the biochemical and enzymatic parameters of mildly diabetic mice (type 2 diabetes mellitus) that still had functional beta cells in order to correct the hyperglycemia and hyperlipidemia associated with diabetes. Low (200 mg/kg BW), middle (400 mg/kg BW) and high (600 mg/kg BW) doses of the ES solution extracts were used to evaluate the hypoglycemic effects in streptozotocin-induced diabetic mice (Van De Laar et al. 2005). Furthermore, this study investigated the association between

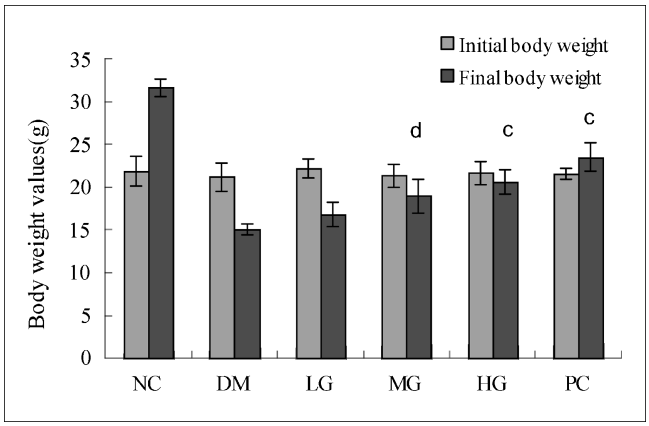

Fig. 1: Body weights at the end of the experiment were compared among all the groups. NC, normal control group (physiological saline); MD, model diabetic mice group (physiological saline); LG, low-dose ES extract group (200 mg kg^{-1} BW); MG, middle-dose ES extract group (400 mg·kg^{-1} BW); HG, high-dose ES extract group (600 mg·kg^{-1} BW); and PC, positive control group (glimepiride solution). In addition to the oral administration, all mice were fed with the normal columnar diet. The data were presented as the means ± S.D, n = 5. Compared with the MD group, b means that the difference is significant ($p < 0.05$), a means that the difference is higher ($p < 0.01$), and other means that the difference is not significant ($p > 0.05$)

glucose and lipid metabolism in type 2 diabetic mice and then studied the possible regulatory mechanism of the insulin resistance in type 2 diabetic mice.

2. Investigations and results

2.1. Changes in body weight

After 4 weeks of the ES extract treatment, the body weight values of each group were evaluated at the beginning and end of this experiment. The experimental data were analyzed, and the results were as follows (Fig. 1):

After the experiment, the normal control (NC) group without the STZ injections grew well. At the same time, the body mass in the model diabetic (MD) group was significantly lower than that in the NC group, but after management with the ethanol extract from ES and treatment with glimepiride, their body weight increased. Compared with the MD group, the differences in the low-dose (LG) group were not significant ($p > 0.05$). At the end of week 4, the body weights of the MG mice were near that of their initial weight, and there was a significant ($p < 0.05$) difference in the diabetic groups compared with MG group. Moreover, the body weights of the mice in the high-dose (HG) ES extract and positive control (PC) groups were higher ($p < 0.01$) than that of the MD groups; however, the HG mice were similar to the PC mice.

2.2. Effect of the ES extract on the organ index

Table 1 shows that, compared with normal mice, the liver, kidney and spleen of the diabetic mice were significantly enlarged at 1.5, 1.6 and 1.4 times that of normal mice, respectively. In the PC group, the index of the liver, kidney and spleen had a highly significant ($p < 0.01$) downward trend, and obvious changes in the liver index were observed in particular.

The treatment of these diabetic mice with the ES extract led to a decline in the percentage of liver index by 14% and 23% for the MG and HG groups, respectively ($p < 0.01$), compared with the diabetic controls, and resulted in a significant recovery of the liver level, returning to the control level.

The inhibitory effect of the kidney and spleen levels of the ES extract on the diabetic mice was also investigated. HG led to a significant ($p < 0.05$) elevation in the kidney and spleen levels compared with their diabetic counterpart, but the improvement was only marginal in the LG and MG mice (not significant).

2.3. Fasting blood glucose and insulin responses

The fasting blood glucose (FBG) response was investigated for 4 weeks in the streptozotocin-induced diabetic and normal mice (Fig. 2). In the NC group, the fasting blood glucose values were normal from the beginning to the end of the experiment, whereas the other results of injecting a low dose of STZ were the mild destruction of the islet B cells and elevation of the blood glucose levels.

Although the streptozotocin injection rapidly induced hyperglycemia after a 4-week treatment with the ES extract, blood glucose levels were reduced. The reduced levels of the FBG concentrations (MG 28%, HG 41%) were almost as small as those of the glimepiride control (51%) mice. The more concentrated the extract, the more the values were reduced. The statistical analysis of the HG and PC groups are significantly different from the initial blood glucose data ($P < 0.01$). Obviously, the ES diet can regulate the blood glucose metabolism.

The fasting serum insulin (FINS) concentrations are shown in Table 2. However, until the end of the experiment, the fasting serum insulin of the middle-dose (MG) groups barely reached the level of the high-dose (HG) group, which was higher ($p < 0.05$) when including low-dose (L) ES extract mice versus the MD mice. The fasting serum insulin of the HG mice was similar to that of the PC mice, and both were significantly higher ($p < 0.01$) than the MD mice. The insulin sensitivity index (ISI) was assessed by the same formula in all groups. The ISI in the glimepiride group and high-dose feeding group was significantly higher than that in the model group ($p < 0.01$), with both nearing the normal level.

The changes in the FINS and ISI suggested that a high-dose extract of the *Euryale* shell might restore the function of the

Table 1: Index of different organs before and after the administration of the triterpenoid-rich fraction of Euryale shells in streptozotocin-induced diabetic mice

Treatment Group	Liver index (mg/g)	Kidney index (mg/g)	Spleen index (mg/g)
NC	40.12 ± 1.48	5.20 ± 0.26	2.53 ± 0.15
DM	60.03 ± 1.35	8.16 ± 0.13	3.87 ± 0.42
LG	56.03 ± 2.52	7.89 ± 1.05	3.97 ± 0.21
MG	52.31 ± 2.80[b]	6.83 ± 0.95	3.27 ± 0.21
HG	46.74 ± 2.13[a]	6.13 ± 1.04[b]	2.87 ± 0.25[b]
PC	44.06 ± 2.10[a]	5.75 ± 0.78[a]	2.70 ± 0.10[a]

Organ index (mg/g) = (mice liver, kidney and spleen weight/body weight of mice) × 100%. Each value represents the mean ± S.D. (n = 5). a and b represents statistical significance ($p < 0.05$) and higher significance ($p < 0.01$) compared with the MD groups, respectively, among each class of index.

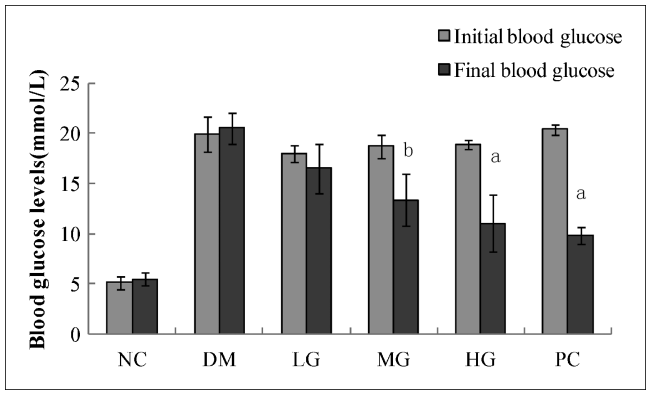

Fig. 2: FBG at the end of the study were compared among all the groups. NC, normal control group (physiological saline); MD, model diabetic mice group (physiological saline); LG, low-dose ES extract group (200 mg·kg^{-1} BW); MG, middle-dose ES extract group (400 mg·kg^{-1} BW); HG, high-dose ES extract group (600 mg·kg^{-1} BW); and PC, positive control group (glimepiride solution). In addition to the oral administration, all mice were fed with the normal columnar diet. The data are presented as the means ± S.D., n = 5. Compared with the MD group, b means that the difference is significant ($p < 0.05$), a means that the difference is higher ($p < 0.01$), and other means that the difference is not significant ($p > 0.05$)

islet beta-cells and reduce the insulin resistance by regulating the level of insulin secretion, indicating it could help improve the status of the diabetic mice despite the fact that the effect was not as good as glimepiride.

2.4. Comparison of lipid values after treatment

The serum TC and TG levels were significantly elevated (21% and 62%, respectively) in the diabetic mice groups compared with the normal controls (Table 3). The supplementation with the ES extract for 4 weeks in the MD mice resulted in a significant diminution of these parameters ($p < 0.05$), and the levels of these parameters returned to the control level. In particular, the TC concentrations in the HG group had the levels reduced below the normal level more effectively ($p < 0.01$) than the PC group. Other hyperlipidemic parameters such as the serum LDL cholesterol were mildly elevated in the MD diabetic groups (Table 3) but decreased significantly ($p < 0.05$) in the extract-supplemented groups.

HDL cholesterol, a healthy lipoprotein, was decreased in the MD groups compared with the control (Table 1). After 4 weeks of treatment with the ES extract, there was a highly significant elevation ($p < 0.01$) of this lipoprotein level in both the HG and PC groups. The improvement in the HDL levels was not significant in the LG and MG groups.

Table 2: FBG, FINS and ISI in the streptozotocin-induced diabetic mice in response to the ES extract treatment

Treatment Group	FBG (mmol/L)	FINS (mIU/L)	ISI
NC	5.45 ± 0.66	4.833 ± 0.603	–3.273 ± 0.032
DM	20.50 ± 1.59	9.301 ± 0.346	–5.247 ± 0.095
LG	16.52 ± 2.45	8.721 ± 0.608	–4.967 ± 0.221
MG	13.32 ± 2.58[b]	7.310 ± 0.436[b]	–4.577 ± 0.231[b]
HG	11.02 ± 2.88[a]	6.133 ± 0.252[a]	–4.210 ± 0.050[a]
PC	9.81 ± 0.88[a]	5.900 ± 0.265[a]	–4.070 ± 0.050[a]

The insulin sensitivity index (ISI) was calculated as ln(1/fasting blood glucose × fasting serum insulin). Each value represents the mean ± S.D. (n = 5). a and b represent statistical significance ($p < 0.05$) and higher significance ($p < 0.01$) compared with the MD groups, respectively, and other means that the difference is not significant ($p > 0.05$).

3. Discussion

In diabetes mellitus, hyperglycemia is usually caused by low insulin levels (type 1 diabetes mellitus) or by resistance to insulin at the cellular level (type 2 diabetes mellitus), depending on the type and state of the disease. We know that the elevation of blood glucose associated with the amount of insulin and the lack of insulin may lead to type 2 diabetes (De Fronzo et al. 1997).

The present investigation reports the hypoglycemic and hypolipidemic effects of the extract of *Euryale* shells (ES) on STZ-induced diabetic mice. The main aim of this study was to assess the multiple roles of an ES ethanol extract as an anti-diabetic agent for the correction of T2MD or NIDDM in mice that have only partial degeneration of beta cells of islets of Langerhans like other natural products have shown (Vessal et al. 2003; Sharma et al. 2003).

The extract used was the triterpenoid-rich extract from the Euryale shell and had been used as the experimental material to evaluate the anti-diabetic function on streptozotocin-induced type 2 diabetic mice. The results showed that the ES extract could inhibit organ enlargement caused by diabetes and restored the essential function of the liver and kidney. Moreover, the results in this study also demonstrated that the ES extract at a level of 600 mg/kg BW provided a protective effect to the diabetic mice similar to glimepiride and enhanced the insulin sensitivity index (ISI), which improved insulin resistance (Matveyenko et al. 2006). Low insulin levels or insulin resistance prevent the body from converting glucose into glycogen, which in turn makes removing excess glucose from the blood difficult or impossible (Leahy 2005). In addition to the dose-dependence, changes in the lipid profile play an important role in the improvement of insulin resistance (IR). Gong et al. (2004) found that resistin could promote the differentiation of anterior adipose cells, which might be an important factor to induce insulin resistance from obesity.

There were a number of controversial issues regarding the effect of the ES triterpenoid-rich extract on blood glucose management. One was the dose-response, with a low dose having little contribution to the treatment of diabetic mice and a high dose potentially causing unadaptable changes. The other was that the IR mechanism was also related to protein kinase, mitogen activated protein and phosphatidylinositol 3-kinase, but the regulatory mechanism needs further study (Song et al. 2002; One et al. 2001; Gedulin et al. 2005).

Above all, the triterpenoid-rich extract from *Euryale* shell had less adverse effects and would be more convenient practically compared with treatments suggested by the traditional medical system for the therapy of diabetes mellitus. Therefore, the triterpenoid-rich extract from *Euryale* shell could be considered effective for the treatment of T2DM to some degree and would be a good functional food ingredient.

4. Experimental

4.1. Preparation of the triterpenoid-rich extract of the Euryale shell

Euryale shells were collected in and around Huainan City. The broken shells of the *Euryale* seed were thoroughly washed with water and dried in the shade. A total of 500 g of air-dried shells were ground into fine powder and soaked in 75% ethanol at 60 °C for 16 h for the extraction. The extract was concentrated with a vacuum rotary evaporator at 50 °C. The concentrated extract was then diluted with water, and the solution was extracted 3 times with petroleum ether, ethyl acetate and water-saturated butanol, in that order. The extracts were then pooled and concentrated using a rotary evaporator to yield triterpenoid-rich main fractions.

4.2. Materials and chemicals

Streptozotocin was purchased from Sigma Chemical Co. (Nanjing, China). The citrate-citrate buffer solution (25 mg/kg, 1% solution of 0.1 mol/L pH

Table 3: Serum level of different lipids after the administration of ES extracts in streptozotocin-induced diabetic mice

Treatment Group	TC (mmol/L)	TG (mmol/L)	LDL (mmol/L)	HDL (mmol/L)
NC	2.30 ± 0.05	0.81 ± 0.03	1.50 ± 0.01	1.83 ± 0.02
DM	2.89 ± 0.04	1.32 ± 0.04	1.85 ± 0.04	1.27 ± 0.03
LG	2.78 ± 0.07	1.34 ± 0.05	1.90 ± 0.02	1.27 ± 0.07
MG	2.59 ± 0.13^b	1.03 ± 0.13^b	1.68 ± 0.07^b	1.32 ± 0.02
HG	2.38 ± 0.08^a	0.87 ± 0.10^a	1.57 ± 0.02^a	1.64 ± 0.04^a
PC	2.44 ± 0.07^a	0.86 ± 0.05^a	1.54 ± 0.02^a	1.72 ± 0.02^a

Each value represents the mean ± S.D. (n = 5). a and b represent statistical significance ($p < 0.05$) and higher significance ($p < 0.01$) compared with the MD group, respectively, and other represents a difference that is not significant ($p > 0.05$).

4.4 sodium) and glimepiride were purchased from Pharmaceutical Group Co., Ltd. (Anhui, China). All other reagents and chemicals used were of analytical reagent grade.

4.3. Selection of animals and induction of diabetes mellitus

Sixty male mice (weighing 18–20 g, Anhui Medical University, Hefei) were maintained under standard environmental conditions (12:12 h light dark cycles) and fed with a standard diet (Pharmaceutical Technology Co., Ltd., Hefei) and water *ad libitum*. All the experiments were approved by the Animal Experiment Committee of China.

After 1 week of dietary manipulation, a subset of the mice (52) were injected intraperitoneally with a low dose of streptozotocin (100 mg/kg BW) dissolved in 0.1 mol/L citrate buffer (Maiti et al. 2005). The 8 mice used as the normal control (NC) were injected intraperitoneally with the buffer solution. Three days after the STZ injection, diabetic mice were defined as having a plasma glucose level greater than 11.0 mmol/L.

4.4. Experimental design

Except for the normal control group (NC), the 40 mice that had developed T2DM with the closest body weights were chosen. They were randomly divided into five groups of 8 animals each, including the model diabetic mice (MD) group, positive control (PC) group and the extract from ES (Low-dose, LG; Middle-dose, MG; and High-dose, HG) groups (Yoshida et al. 2009).

The normal control (NC) and diabetic mice (MD) were fed with the standard diet, whereas the LG, MG and HG groups received the triterpenoid-rich extract of ES suspended in distilled water orally at doses of 200, 400 and 600 mg/kg, respectively. The positive control (PC) group received 5 mg/kg of glimepiride, used as a reference standard drug. Each treatment lasted for 4 weeks, during which period the mice had free access to food and water.

4.5. Effect of body weight and organ index

The weights of the mice were recorded at the start and end of the experimental period with an electronic balance. After 4 weeks of treatment with the ES extract, the mice were sacrificed under ether anesthesia. The organs were removed from the mice quickly, rinsed in saline water and weighed. The organ index (mg/g) = (mice liver, kidney and spleen weight/body weight of mice) × 100%

4.6. Detection of serum biochemical indicators and calculation of ISI

The mice were fasted for 12 h before sacrifice. Fasting blood glucose was evaluated from the tip of the tail vein using the Roche Glucometer. Fasting serum insulin was measured by magnetic separation enzyme linked immunosorbent assay. The insulin sensitivity index (ISI) was calculated as ln(1/fasting blood glucose × fasting serum insulin).

4.7. Estimation of lipid profile in blood samples

On completion of the treatment, the blood samples were collected, and the lipid profiles of all six groups of animals were measured using commercially available kits. The total cholesterol (TC), high density lipoprotein (HDL) and triglyceride (TG) levels in the serum were determined according to the instructions of the manufacturer.

4.8. Statistical analysis

The statistical software Origin 6.1 (Origin Lab Corporation, USA) was used by the first author in this study. All experimental data were expressed as the means ± S.D. The differences between the test and control groups were evaluated by Student's t-test.

Acknowledgements: The authors gratefully acknowledge the Department of Science and Technology, Anhui Province Natural Science Funds (Sanction NO. 1208085MC56) for supporting this project.

References

Bhaskar A, Vidhya VG, Ramya M (2008) Hypoglycemic effect of Mucuna pruriens seed extract on normal and streptozotocin-diabetic rats. Fitoterapia 79: 539–543.

Bailey LJ, Day C (1989) Traditional plant medicines as treatment for diabetes. Diab Care 12: 553–564.

Sharma B, Balomajumder C, Roy P (2008) Hypoglycemic and hypolipidemic effects of flavonoid rich extract from Eugenia jambolana seeds on streptozotocin induced diabetic rats. Food Chem Toxicol 46: 2376–2383.

Brennan CS, Cleary LJ (2005) The potential use of cereal beta-D-glucans as functional food ingredients. J Cereal Sci 42: 1–13.

De Fronzo RA, Bonadonna RC, et al. (1997) International Textbook of Diabetes Mellitus. Chichester: John Wiley & Son Ltd 1: 635–711.

Gedulin BR, Nikoulina SE, Smith PA, Gedulin G, Nielsen LL, Baron AD, Parkes DG, Young AA (2005) Exenatide (exendin-4) improves insulin sensitivity and B-cell mass in insulin resistant obesefalfa Zucker rats independent of glycemia and body weight. Endocrinology 146: 2069–2070.

Gong H, Ni Y, Guo X, Fei L, Pan X, Guo M, Chen R (2004) Resistin promotes 3T3-Ll preadipocyte differentiaion. Eur J Endocrinol 150: 885–892.

Huang THW, Peng G, Kota BP, Li GQ, Yamahara J, Roufogalis BD, Li Y (2005) Anti-diabetic action of Punica granatum flower extract: activation of PPAR-c and identification of an active component. Toxicol Appl Pharmacol 207: 160–169.

Kim H, Stote KS, Behall KM, Spears K, Vinyard B, Conway JM (2009) Glucose and insulin responses to whole grain breakfasts varying in soluble fibre: A dose–response study in obese women with increased risk for insulin resistance. Eur J Clin Nutr 48: 170–175.

King H, Aubert RE, Herman WH (1998) Prevalence, numerical estimates, and projections. Diabetes Care 21: 1414.

Leahy JL (2005) Beta-cell dysfunction in type 2 diabetes melllitus. Joslin's Diabetes Mellitus. 14th ed. Philadelphia 1: 449–462.

Lee SE, Ju EM, Kim JH (2002) Antioxidant activity of extracts from Euryale ferox seed. Exp Mol Med 34: 100–106.

Maiti R, Das UK, Ghosh D (2005) Attenuation of hyperglycemia and hyperlipidemia in streptozotocin induced diabetic rats by aqueous extract of seed of Tarmarindus indica. Biol Pharm. Bull 28: 1172–1176.

Matveyenko AV, Butler PC (2008) Relationship between Beta-cell mass and diabetes onset. Dibetes, Obesity and Metab 10: 28–31.

Nath BK, Chakraborty AK (1985) Studies on amino acid composition of the seeds of Euryale ferox Salisb. Food Sci Technol 22: 293–296.

Oliveira ACP, Endringer DC, Amorim LAS, Brandão MGL, Coelho MM (2005) Effect of the extracts and fractions of Baccharis trimera and Syzygium cumini on glycemia of diabetic and non-diabetic mice. J Ethnopharmacol 102: 465–469.

Ono H, Katagiri H, Funaki M, Anai M, Inukai K, Fukushima Y, Sakoda H, Ogihara T, Onishi Y, Fujishiro M, Kikuchi M, Oka Y, Asano T (2001) Regulation of phosphoinositide metabolism, Akt phosphorylation and glucose transport by PTEN (phosphatase and tensin homolog deleted on chromosome l0) in 3T3-Ll adipocytes. Mol Endocrino 15: 1411–1422.

Row LC, Ho JC, Chen CM (2007) Cerebrosides and tocopherol trimers from the seeds of Euryale ferox. J Nat Prod 70: 1214–1217.

Sharma SB, Nasir A, Prabhu KM, Dev G, Murthy PS (2003) Hypoglycemic and hypolipide-mic effect of ethanolic extracts of seeds of E. Jambolana

in alloxan-induced diabetic model of rabbits. J. Ethnopharmacol 85: 201–206.

Song H, Shojima N, Sakoda H Ogihara T, Fujishiro M, Katagiri H, Anai M, Onishi Y, Ono H, Inukai K, Fukushima Y, Kikuchi M, Shimano H, Yamada N, Oka Y, Asano T (2002) Resistin is regulated by C/EBP, PPARs, and signal-transducing molecules. Biochem Biophys Res Commun 299: 291–298.

Tahrani AA, Piya MK, Kennedy A, Barnett AH (2010) Glycaemic control in type 2 diabetes: Targets and new therapies. Pharmacol Ther 125: 328–361.

Topping D (2007) Cereal complex carbohydrates and their contribution to human health. J Cereal Sci 46: 220–229.

Van De Laar FA, Lucassen PL, Akkermans RP, Van De Lisdonk EH, Rutten GE, Van WC (2005) Alpha-glucosidase inhibitors for patients with type 2 diabetes: Results from a cochrane systematic review and meta-analysis. Diabetes Care 28: 154–163.

Vessal M, Hemmati M, Vasei M (2003) Antidiabetic effects of quercetin instreptozocin- induced diabetic rats. Comp Biochem Physiol Part C 135: 357–364.

Wood PJ (2007) Cereal beta-glucans in diet and health. J Cereal Sci 46: 230–238.

Yasuda K, Shimowada K, Uno M, Odaka H, Adachi T, Shuhara N (2003) Long-term therapeutic effects of voglibose, a potent intestinal alphaglucosidase inhibitor, in spontaneous diabetic GK rats. Diabetes Res Clin Pract 59: 113–122.

Yoshida T, Okuno A, Tanaka J, Takahashi K, Nakashima R, Kanda S, Ogawa J, Hagisawa Y, Fujiwara T (2009) Metformin primarily decreases plasma glucose not by gluconeogenesis suppression but by activating glucose utilisation in a non-obese type 2 diabetes Goto-Kakizaki rats. Eur J Pharmacol 623: 141–147.

Zhao HR, Zhao SX, Guillaume D, Sun C (1994) New cerebrosides from Euryale ferox. J Nat Prod 57: 138–142.