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Full Length Research Paper

Antidiabetic effect of burdock (*Arctium lappa* L.) root ethanolic extract on streptozotocin-induced diabetic rats

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Antidiabetic effect of the root ethanolic extract of burdock (*Arctium lappa* L.), a traditional medicinal and edible plant, was investigated in streptozotocin- induced diabetic rats. The results show that the oral administration of burdock root ethanolic extract (BRE) significantly decreased blood glucose and increased insulin level in diabetic rats compared to the control diabetic group. Meanwhile, the levels of serum total cholesterol (TC), triglycerides (TG) and low density lipoprotein (LDL) in the BRE treated diabetic rats were lower, and the high density lipoprotein (HDL) level was higher than those index of the control diabetic rats. Furthermore, oral administration of BRE significantly decreased serum urea and creatinine as well as malondialdehyde (MDA) levels of liver and kidney tissues, while body weight gain and tissue glycogen content were elevated in diabetic rat, all of which indicate an improvement in diabetic state. In addition, 400 mg/kg body weight BRE treated group had a marked improvement of the glucose tolerance in normoglycemic rats. No hypoglycemic effects of BRE were observed in normal rats. The results demonstrate that BRE possessed significant antidiabetic activity in diabetic rats.

Key words: Burdock root, ethanolic extract, antidiabetic effect.

INTRODUCTION

Diabetes mellitus is a metabolic disorder in the endocrine system with hyperglycemia and carbohydrate, protein and fat metabolism disturbances, due to absolute or relative deficiency of insulin secretion (Oliveira et al., 2008). The high morbidity and fatality as well as significant costly and financial burden of this dreadful disease are becoming a serious threat to mankind health (Wild et al., 2004). Various studies have shown that diabetes mellitus is associated with increased formation of free radicals and decrease in antioxidant potential due to persistent hyperglycemia. This leads to oxidative damage of cell components such as proteins, lipids and nucleic acids (Rolo and Palmeira, 2006).

Besides, drugs classically used for the treatment of diabetes include, insulin, sulphonylureas, biguanides and thiazolidinediones. Recently, many investigations indicated that supplementation with nature antioxidants may alleviate the oxidative damage in diabetes (Nazıroğlu and Butterworth, 2005; Kamalakannan and Prince, 2006). In particular, it is recognized that consumption of natural antioxidants of fruits, vegetables and grains are important for the prevention of chronic illnesses in diabetes patients (Dixit and Kar, 2005; Singh and Rajini, 2005). A considerable interest has grown in finding both hypoglycemic and antioxidative properties of natural antioxidants for the treatment of diabetes (Rahimi et al., 2005). Burdock (*Arctium lappa* L.) is an edible plant

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Abbreviations: STZ, Streptozotocin; **BRE,** burdock root ethanolic extract; **b.w,** body weight; **HDL,** high density lipoprotein; **LDL,** low density lipoprotein; **MDA,** malondialdehyde.

used in traditional medicine of the Asteraceae (Compositae) family. Its root is commonly eaten as food by people in East Asia. Root of burdock exhibit a wide range of biological activities covering anti-inflammatory (Lin et al., 1996), free radical scavenging activities (Chen et al., 2004) and antiallergic activity (Knipping et al., 2008).

Studies on the antidiabetic effect of burdock root are few and the results of such studies are inconsistent. Silver et al. (1931) investigated the effect of burdock powder on normal and diabetic patients, and found out that burdock root possess hypoglycemic effect considered as polysaccharides, a mainly component of the root which keep the blood glucose level constant, therefore improving the tolerance to high glucose level. However, Swanston-Flatt et al. (1989) reported that oral administration of burdock decoction for 28 days aggravated the diabetic condition in streptozotocin (STZ)-induced diabetes mice. So far, no reliable studies have been carried out on the efficacy of burdock root in experiment animal, and its possible antidiabetic effect is not understood completely (Natural Standard Systematic News, 2002). Hence, this paper was designed to investigate antidiabetic and antioxidant activity of burdock root ethanolic extract in STZ-induced diabetic rats.

MATERIALS AND METHODS

Preparation of burdock root ethanolic extracts (BRE)

Fresh roots of burdock were cleaned, dried in shade and finely powdered. The powder was defatted with petroleum ether and then extracted with 70% ethanol (1:10, w/v) for 72 h at room temperature. Filtered with Whatman paper No.1 and the residue was re-extracted twice till exhaustion, the combined filtrates was concentrated under vacuum at 50°C and the resulting filtrate were freeze-dried (Boyikang Refrigerated Vapor Trap, SD-1A-50). The extract yield was 16.5% (w/w); the obtained extract was stored at -20°C until use.

Determination of total phenolic content and total flavonoid content

The total phenolic contents of BRE were measured using a modified Folin–Ciocalteu method (Singleton et al., 1999). The value obtained for the total phenolic content was expressed in milligrams of gallic acid equivalents (GAE) per 1 g of extract. The total flavonoid contents of BRE were measured using a modified colorimetric method (Jia et al., 1999). The values were expressed as milligrams of quercetin equivalents (QE) per 1 g powder of extract.

Animals

Six to eight week old male Sprague-Dawley rats (weighing 150 to 180 g) were obtained from the Animal Experimental Center of College of Medicine, Shandong University. They were kept in individual cages, and maintained under 12/12 h light/dark cycles at room temperature (22 to 25°C). All animals were carefully monitored and all the experimental protocol with the animals was in accordance with the internationally accepted principles for laboratory animal use and the experimental protocols duly approved by the Institutional Ethical Committee.

Acute toxicity study

Healthy adult Sprague-Dawley albino rats of either sex, starved overnight were divided into four groups, each consisting of five rats and were orally fed with the BRE in increasing dose levels of 100, 500, 1000 and 3000 mg/kg body weight (b.w). The animals were observed continuously for 72 h.

Assessment of hypoglycemic potential in normal rats

The fasting blood glucose level evaluation was performed in overnight fasted (18 h) normal rats (Kar et al., 2006). Rats were divided into three groups of six normal rats. Group 1 served as untreated control and was given distilled water only. Groups 2 and 3 received doses of 200 and 400 mg/kg b.w. BRE, respectively. Blood samples were collected at 0, 30, 60, 120 and 180 min, after BRE administration to determine fasting blood glucose level with a glucometer (glucometer JPS-X, Beijing Yincheng Bioelectronics Technology Co. Ltd, China). The oral glucose tolerance test was performed in overnight fasted (18 h) normal rats (Salahuddin and Jalalpure, 2010). Rats were divided into four groups; each consisting of six rats and were administered 0.9% (w/v) saline, glibenclamide 2.5 mg/kg b.w. (glibenclamide was used as the standard drug), BRE 200 and 400 mg/kg b.w., respectively. Glucose (3 g/kg b.w.) was fed 30 min after the administration of BRE. The tail vein blood was collected at 0, 30, 60, 120 and 180 min of glucose administration to determine blood glucose level.

Preparation of diabetic rats

Diabetic rats were induced in overnight fasted rats by a single intraperitoneal injection of 70 mg/kg b.w. STZ (Liu et al., 2006). The STZ was freshly dissolved in 0.1 M citrate buffer (pH 4.5). On the third day after administration of STZ, the blood from tail vein was collected to determine fasting blood glucose level; above 250 mg/dl was considered diabetic.

Experimental design and treatment schedule

24 diabetic rats and six normal rats were randomly divided into five groups (n = 6). The extract was administered for 14 days. They included: group I: normal control rats administered saline (0.9%, w/v); group II: diabetic control rats administered saline (0.9%, w/v); group III: diabetic rats administered glibenclamide (2.5 mg/kg b.w.) daily for 14 days; group IV: diabetic rats administered BRE (200 mg/kg b.w.); and group V: diabetic rats administered BRE (400 mg/kg b.w.).

The effects of administration of BRE in diabetic rats were observed by measuring fasting blood glucose, serum insulin, lipid profile, urea and creatinine; liver and skeletal muscle glycogen content, the lipid peroxidation (MDA) of liver and kidney tissues and changes in body weight. Fasting blood glucose was estimated on day 0, 3, 7 and 14 of BRE administration. The other biochemical parameters were determined on day 15 after the animals were sacrificed by decapitation. Serum insulin level was estimated by using a commercial diagnostic radio immunoassay kit (Beijing North Institute of Biological Technology, China). Serum lipid profiles, urea and creatinine level were measured by an auto analyzer (Unicel DXC 800 auto biochemistry analyster, Beckman, USA). Liver and skeletal muscle glycogen content was measured according to an

Table 1. Hypoglycemic effect of burdock root ethanolic extract on normal rats.

Test model	Group	Dose (mg/kg.b.w.)	Mean blood glucose concentration (mg/dL) ±S.E.M. inhibition (%)				
			0 h	1/2 h	1 h	2 h	3 h
NG	Control	-	100.3±3.7	106.5±4.3	104.5±4.9	105.5±4.6	102.5±2.7
	BRE	200	110±2.5	111.5±4.2	107.5±3.2	103.3±5.4	104.3±5.9
		400	109.7±7.5	114.5±5.5	110±2.5	109±3.9	100.8±4.5
OGTT	Control	-	111.5±4.2	168.8±7.7	148.8±6.9	127.8±3.4	118.0±4.2
	Glibenclamide	2.5	105.5±4.6	152.0±7.2* (9.9)	129.3±6.0* (13.1)	104.3±6.0** (18.4)	85.8±7.4** (27.3)
	BRE	200	113.8±4.3	163.8±9.0 (2.9)	137.8±5.7 (7.9)	121.5±3.5 (4.9)	116.0±4.3 (2.1)
		400	112.0±7.4	157.7±8.3 (6.6)	131.3±4.7* (11.8)	117.0±3.4 (8.5)	112.7±4.6 (4.9)

NG, Normoglycemic; OGTT, oral glucose tolerance test; S.E.M, mean standard error; n = 6 (number of animals in each group), significant difference from control. Statistical significance between means was assessed using one-way analysis of variance followed by Duncan's test as a post-analysis of variance test; *p <0.05; **p <0.01.

earlier reported method (Borst et al., 2000). The lipid peroxidation (MDA) of liver and kidney tissues was measured by using commercial diagnostic kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Statistical analysis

Data were statistically evaluated using one-way analysis of variance followed by Duncan's test as a post-analysis of variance test. The values were considered significant when $p<0.05$.

RESULTS

Total phenolic and flavonoid content

The total phenolic and flavonoid content in BRE was found to be 19.78 mg GAE/g and 12.53 mg QE/g, respectively.

Acute toxicity study

Acute toxicity study revealed the non-toxic nature of the BRE. There was no lethality or any toxic reactions found at any of the doses selected until the end of the study period.

Oral glucose tolerance test (OGTT)

The hypoglycemic effects of oral administration of BRE on OGTT of normal rats are shown in Table 1; the maximum rise in blood glucose occurred 30 min after the oral glucose challenge. There was a 11.8% decrease ($P<0.05$) of blood glucose levels with 400 mg/kg b.w. BRE at 60 min after glucose administration and returned to normal level by 3 h. Glibenclamide was found to decrease blood glucose level continuously and the maximum decrease of blood glucose level was 27.3% at 3 h after glucose administration.

Hypoglycemic effect of BRE

In order to determine the sub acute effects, two doses of BRE were administered throughout 14 days consecutively. The blood glucose level of each animal was monitored on 0, 3, 7 and 14 days after the administration of the test samples. As shown in Table 2, the initial antidiabetic activity was observed on the 7th day and continued to increase in all groups during the experimental period. At the end of 14 days of treatment, there was a decrease (31.5%, $P<0.01$) of blood glucose levels with 400 mg/kg b.w. BRE treated group; the standard drug glibenclamide also caused a significant decrease (34.7%) of blood glucose levels, while normal rats did not exhibit any significant alterations in blood glucose levels during the experiment (Table 1).

Body weight, serum insulin, liver and skeletal muscle glycogen

There was a decrease in the serum insulin, muscle and liver glycogen contents of diabetic rats when compared to normal rats (Table 3). When BRE was administered to diabetic rats for 14 days, the serum insulin, muscle and liver glycogen contents increased significantly compared to the control diabetic rats. Significant weight loss was observed in diabetic rats compared to normal rats. The administration of BRE or glibenclamide improved the body weight as compared to the control diabetic rats.

Serum lipid profile

There was a significant decrease in the level of serum high density lipoprotein (HDL) and a significant increase in the levels of total cholesterol, triglycerides and low

Table 2. Hypoglycemic effect of burdock root ethanolic extract on diabetic rats.

Group	Dose (mg/kg b.w.)	Mean blood glucose concentration (mg/dL) ±S.E.M. (inhibition %)			
		0 day	3th day	7th day	14th day
Control	-	116.3±7.3	105.3±8.1	117.7±7.8	114.8±6.0
Diabetic	-	382.8±23.9	362.3±22.1	344.7±19.2	355±18.2
Glibenclamide	2.5	363.0±21.2	311.3±11.9	260.3±11.2** (28.2)	237.0±22.6** (34.7)
BRE	200	363.3±22.1	342.8±16.3	297.8±21.9 (18.1)	265.8±30.5** (26.8)
	400	366.3±23.5	321.5±9.8	270.3±22.1** (25.6)	249±31.4** (31.5)

S.E.M, Mean standard error. n = 6 (number of animals in each group), significant difference from diabetic control. Statistical significance between means was assessed using one-way analysis of variance followed by Duncan's test as a post-analysis of variance test; *p <0.05; **p <0.01.

Table 3. Effect of burdock root ethanolic extract on serum insulin level, liver and skeletal muscle glycogen and changes in the body weight of diabetic rats.

Group	Dose (mg/kg b.w.)	Glycogen(mg/g wet tissue)		Serum insulin (μ U/ml)	Body weight	
		Liver	Skeletal muscle		Initial (g)	Final (g)
Control	-	85.49 ±2.94**	27.99±1.43**	111.44± 13.47**	165.9±2.1	188.6±1. 7**
Diabetic	-	35.01 ± 2.65	16.91±0.96	31.36± 5.43	165.6±3.2	136.3±4.2
Glibenclamide	2.5	57.93 ±4.28**	25.78± 0.85**	55.31± 6.28**	167.3±3.7	154.8±3.7**
BRE	200	41.96 ± 2.16	21.35±0.94	47.03± 5.42*	164.6±3.3	143.8±2.2
	400	55.90 ± 2.57*	25.16± 0.85**	52.83 ± 5.81 **	164.1±3.0	153.3±2.6**

Data are mean±S.E.M. S.E.M.: mean standard error; n = 6 (number of animals in each group), significant difference from diabetic control. Statistical significance between means was assessed using one-way analysis of variance followed by Duncan's test as a post-analysis of variance test.; *p <0.05; **p <0.01.

density lipoprotein (LDL) in diabetic rats compared to normal rats. The administration of BRE and glibenclamide significantly decreased the serum triglycerides, total cholesterol and LDL levels, and increased the HDL levels compared to the control diabetic rats (Table 4).

Changes of serum urea and creatinine

It can be seen in Table 5 that there was a significant elevation in serum urea and creatinine in the diabetic control rats as compared with the normal rats group. The administration of BRE and glibenclamide significantly decreased serum urea and creatinine, when compared with control diabetic rats.

The lipid peroxidation (MDA) of liver and kidney tissues

In Table 5, there was a significant elevation in MDA of liver and kidney tissues in the diabetic rats as compared with the normal rats. The administration of BRE and glibenclamide significantly decreased MDA levels of liver and kidney tissues, when compared with control diabetic rats.

DISCUSSION

The study results showed that BRE had a marked hypoglycemic activity by lowering the blood glucose levels in STZ-induced diabetic rats, and by the improvement of the glucose tolerance but not fasting blood glucose in normoglycemic rats. STZ is an antibiotic that can cause pancreatic β-cell destruction. STZ-induced diabetic rat is one of the animal models of insulin dependent diabetes mellitus or type I diabetes mellitus. In this model, STZ significantly induced hyperglycemia accompanied by hypoinsulinemia, which arises from irreversible destruction of the β-islet cells of the pancreas through its generation of cytotoxic oxygen free radicals (Szkudelski, 2001). In this study, oral administration of BRE 14 days produced a significant increase in insulin levels along with a decrease in blood glucose levels in STZ-induced diabetic rats, exhibiting its protective potential for regulating diabetes mellitus.

The elevation in serum insulin levels may be due to substances present in BRE which promote insulin secretion by the stimulation of a regeneration process and protect the remaining beta cells from further deterioration. Under normal conditions, insulin promotes intracellular glycogen deposition by stimulating glycogen synthase (Eliza et al., 2009) in the diabetic state due to

Table 4. Effect of burdock root ethanolic extract on serum lipid profile in diabetic rats.

Group	Dose (mg/kg b.w.)	Serum lipid profile (mg/dl)			
		TG	TC	HDL	LDL
control	-	0.80 ± 0.08**	0.91 ± 0.33**	0.71 ± 0.07**	0.24 ± 0.02**
Diabetic	-	1.29 ± 0.13	1.31 ± 0.10	0.45 ± 0.04	0.42 ± 0.04
Glibenclamide	2.5	0.8 ± 0.10**	0.96 ± 0.07**	0.67 ± 0.05**	0.28 ± 0.03**
BRE	200	1.07 ± 0.12	1.13 ± 0.12	0.61 ± 0.06	0.33 ± 0.04
	400	0.95 ± 0.14 **	0.97 ± 0.11**	0.66 ± 0.07**	0.29 ± 0.02**

Data are mean ± S.E.M. S.E.M, mean standard error; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; n = 6 (number of animals in each group), significant difference from diabetic control. Statistical significance between means was assessed using one-way analysis of variance followed by Duncan's test as a post-analysis of variance test; *, <0.05, **p <0.01.

Table 5. Effect of burdock root ethanolic extract on liver and kidney MDA, serum urea and creatinine in diabetic rats.

Group	Dose (mg/kg b.w.)	Serum urea (mmol/L)	Serum creatinine (µmol/L)	MDA (nmol/mg protein)	
				Liver	Kidney
Control	-	7.22 ± 0.43 **	25.75 ± 0 .51**	2.36 ± 0.23**	2.23 ± 0.35**
Diabetic	-	14.69 ± 0.33	35.97 ± 1.35	3.51 ± 0.12	3.85 ± 0.21
Glibenclamide	2.5	11.54 ± 0.92**	29.72 ± 2.21*	2.85 ± 0.2**	2.89 ± 0.1**
BRE	200	12.06 ± 0.83*	31.45 ± 1.67	3.07 ± 0.15	3.12 ± 0.16*
	400	11.28 ± 0.59**	27.62 ± 1.93**	2.78 ± 0.1**	2.67 ± 0.18**

Data are mean ± S.E.M. S.E.M, mean standard error; n = 6 (number of animals in each group),significant difference from diabetic control. Statistical significance between means was assessed using one-way analysis of variance followed by Duncan's test as a post-analysis of variance test.; *p <0.05, **p <0.01.

lack of insulin which results in the inactivation of glycogen synthase system as well as reduced insulin-induced glucose utilization by the tissues (Munoz et al., 1996). In this study, it was shown that hepatic and skeletal muscle glycogen content reduced drastically in STZ-diabetic rats. Treatment of BRE to diabetic rats significantly improved glycogen content of liver and muscles. Induction of diabetes with STZ also leads to loss of body weight, which may be due to increased catabolism of glycogen in muscle, liver and loss of tissue proteins (Rajkumar et al., 1991). After 14 days of BRE treatment, body weight of STZ-diabetic rats was improved. An increase in glycogen content and body weight of diabetic rats might be due to an improvement in insulin secretion and glycemic control.

Diabetes mellitus is usually associated with abnormal levels of serum lipids. Hypercholesterolemia and hypertriglyceridemia are primary factors involved in the development of atherosclerosis and coronary heart diseases which are the secondary complications of diabetes (Ananthan et al., 2003). The treatment of BRE to diabetic rats markedly decreased triglycerides, total cholesterol and LDL, but increased HDL. The results indicate that BRE could modulate blood lipid abnormalities, which would be helpful to the prevention of diabetic complications through improving dyslipidemia. Renal impairment is one of the serious and common diabetic complications; the diabetic rats had increased levels of serum urea and creatinine, which are considered as significant markers of renal function impairment (Almdal and Vilstrup, 1988). Treatment with BRE indicated a significant decrease in levels of serum urea and creatinine which could be due to decreased metabolic disturbances as the extract improved glycemic control.

In diabetes, hyperglycemia also further results in the generation of free radicals which can exhaust antioxidant defenses thus leading to the disruption of cellular functions, oxidative damage to membranes and enhanced susceptibility to lipid peroxidation (Li et al., 2010). In the present study, the level of MDA was significantly elevated in liver and kidney tissues of diabetic rats. Treatment with BRE lowered the level of MDA in kidney and liver tissues of diabetic rats, indicating the inactivation of lipid peroxidation reactions and the decreased free radical generation. In a recent study, the chemical characterization of burdock root was studied and was found consisting largely of phenolic acid and flavonoid. Caffeoylquinic acid (chlorogenic acid and dicaffeoylquinic acid) and quercetin are major compounds (Ferracane, 2010); these compounds have been proven to possess powerful antioxidant activities. In addition, chlorogenic acids possess hypoglycemic effect as well as decrease cholesterol and triglycerides levels (Johnston et al., 2003; Cho et al, 2010).

Vessal et al. (2003) found that quercetin promotes β-cell regeneration of the pancreatic islets, and increases

insulin release in STZ-diabetic rats. Sitosterol-beta-D-glucopyranoside, one of steryl glucosides was also isolated from burdock root by Mitsuo et al. (2005), and was found to possess inhibitory effect on alpha glucosidase activities *in vitro*. In this study, our results also show that BRE contained phenolic acid (19.78 mg GAE/g) and flavonoid (12.53 mg QE/g,). Thus, the significant antidiabetic effect of burdock root could be due to the presence of various phytoconstituents which in synergism can impart therapeutic effect.

Conclusion

From this study, we concluded that BRE is beneficial in controlling the blood glucose level, improves the lipid metabolism and prevents diabetic complications from lipid peroxidation in experimental diabetic rats. It has the potential to impart therapeutic effect in diabetes. Acute toxicity studies revealed no toxic effects, therefore, consumption of phenolic and flavonoid containing burdock root used as foods and beverages could be beneficial for the protection and alleviation of diabetic complications. Further experimental study is essential for burdock which could be used as a supplement for the treatment of diabetes mellitus and its complications.

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