Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 1, 2014

Reserch Article

ANTIHYPERGLYCEMIC EFFECT OF *ZINGIBER OFFICINALE* ROSCOE BARK IN STREPTOZOTOCIN-INDUCED TYPE 2 DIABETIC MODEL RATS

SHABAH SHADLI[1,2], MORSHEDUL ALAM[1,3*], ANWARUL HAQUE[1], BEGUM ROKEYA[4], LIAQUAT ALI[5]

[1]Department of Biotechnology and Genetic Engineering, Faculty of Applied Science and Technology, Islamic University, Kushtia-7003, Bangladesh, [2]Department of Psychology & Brain Health Research Center, University of Otago, Dunedin-9054, New Zealand, [3]Department of Gene Expression Regulation, Institute of Development, Aging and Cancer, Tohoku University Graduate School of Medicine, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan, [4]Department of Pharmacology, Biomedical Research Group, BIRDEM, Dhaka-1000, [5]Department of Biochemistry & Cell Biology, Bangladesh University of Health Sciences, Dhaka-1214, Bangladesh. Email: morshedbt@gmail.com

Received: 15 Nov 2013, Revised and Accepted: 20 Dec 2013

ABSTRACT

Objective: The present study evaluates the glucose homeostasis and hypolipidemic properties of ethanol extract of *Z. officinale* in normal and streptozotocin-induced type 2 diabetic model rats.

Methods: Type 2 diabetic model is induced by a single intra-peritoneal injection of streptozotocin (90mg/kg body weight) to 48hr old pulps of Long-Evans rats. Ethanol (50%) extract of *Zingiber officinale* is administered for 42 days at a dose of 1.25-g/kg body weight to type 2 diabetic rats. Blood is collected on 0, 22 and 42 days. Serum glucose is estimated by GOD-POD method, serum insulin by an ELISA, serum lipids by enzymatic-colorimetric, liver glycogen by anthrone sulphuric acid method, creatinine and amino alanine transferase (ALT) by automatic analyzer.

Results: Six weeks administration of ethanol extract of *Z. officinale* results in a significant decrease in fasting serum glucose level in comparison to diabetic control rats (serum glucose, M + SD, mmol/l: 6.9 + 1.0 vs. 8.5 + 0.7, p=0.002). There are 22% and 11% decrease of serum total cholesterol (p=0.036) and TG level after 6 weeks of administration of *Z. officeinale* in comparison to the initial day respectively. Protective HDL cholesterol is increased by 27% and atherogenic LDL cholesterol is decreased by 80% (P=0.04) in comparison to baseline level. Serum insulin level for extract treated groups increases by 92% in comparison to the baseline value and glycogen level is also increased significantly (p=0.002) in comparison to normal control rats. In gut absorption study, the sucrose is loaded (2.5 g/kg body weight) with or without extract to see the inhibitory effect of *Z. officinale* in six different segments of the gastrointestinal tract after 1 hour and 2 hour and no significant changes are observed in the remaining sucrose content among the control and 50% ethanol extract treated group.

Conclusion: The results of the experimental study suggest that *Z. officinale* possesses potent hypoglycemic, insulin secretory and hypolipidemic effects. The antidiabetic effect of *Z officinale* is at least, partly mediated by increasing glycogenesis.

Keywords: *Zingiber officinale,* Glucose homeostasis, Hypolipidemic, Glycogenesis.

INTRODUCTION

In recent years, there has been renewed interest in the treatment of different diseases using herbal drugs as they are generally non-toxic and World Health Organization has also recommended the evaluation of the effectiveness of plants in condition where we lack safe modern drugs. Plant derivatives with hypoglycemic properties have been used in folk medicine and traditional healing systems around the world [1] from the very ancient time. Despite the introduction of hypoglycemic agents from natural and synthetic sources, diabetes and its secondary complications continue to be a major medical problem to people [2]. Medicinal plants used to treat hypoglycemic and hyperglycemic conditions are of considerable interest to ethnobotanical community as they are recognized to contain valuable medicinal properties in different parts of the plant.

Zingiber officinale Roscoe (family, Zingiberaceae), known commonly as ginger, is consumed worldwide in cookeries as spice and flavoring agent [3]. It has been used as spice and medicine for thousands of years. Its use is recorded in early Sanskrit and Chinese texts and is also documented in ancient Greek, Roman and Arabic medical literature [4].

It was reported that ginger juice has significant blood glucose lowering effect [5, 6]. Furthermore, a decreased blood glucose and urea were also observed by other investigators [7]. Ginger also decreased LDL-cholesterol, VLDL-cholesterol and triglycerides levels in apolipoprotein-E deficient mice [8]. Bhandari *et al*., [9] have demonstrated that the ethanol extract of ginger prevent hypercholesterolemia and development of atherosclerosis in cholesterol-fed rabbits. As many scientists showed decreased blood glucose and lipidemic status but the underlying mechanism is not still disclosed. So, there is still a scope to study the mechanism that works underneath these beneficial effects. Thus, considering the versatile medicinal values of ginger, the present study was undertaken to evaluate mechanism of the glucose homeostasis as well as the lipidemic status in normal and STZ induced type 2 diabetic model rats.

MATERIAL AND METHODS

Plant materials and preparation of test sample

The barks of *Zingiber officinale* were collected from Mirpur, Dhaka, Bangladesh. The plant was identified and kept in Biotechnology & Genetic Engineering department, Islamic University, Kushtia, Bangladesh for future reference. The rhizome were cut into small pieces and then water washed carefully. After washing, the fresh rhizome was air-dried (away from sunlight) and then oven dried at 40°C temperature. The dried rhizome is then grinded to make powder, which were then screened to get fine powder. Rhizome (3500g) dried in oven yielded 700 g of *Zingiber officinale* powder. The dried rhizome powder (500g) was soaked in 50% ethanol. These suspensions were filtered with thin and clean cloth and then filtered by filter paper. The suspensions were evaporated by BUCHI Rota vapor R-114 [BUCHI, Germany], connected with BUCHI water bath B-480 at 50^{0}C. In this case, 175mbar (to remove ethanol), 72mbar (to remove water) pressure and 160rpm rotation speed were maintained constantly. Finally, freeze-drier (HETOSICC, Heto Lab Equipment, Denmark) was used to get the dried powder and 83 g of ethanol extracts were obtained.

Experimental Animals

The study was conducted with adult female Long-Evans rats (weighing 180-220g). They were bred at the BIRDEM animal house maintained at a constant room temperature of 22±5^{0}C, 40-70% humidity conditions and the natural day-night cycle with an *ad libitum* access to food except the day of experimental procedure when animals were used after 12hrs fasting. The rats had no access

to food during the whole period of blood sampling. The influence of circadian rhythms was avoided by starting all experiments at 7.30 a.m.

Induction of Type 2 Diabetes to the Rats

Type 2 diabetes was induced by a single intra-peritoneal injection of streptozotocin (90mg/kg body weight, dissolved in 0.1M citrate buffer, pH 4.5) to 48hr old pulps of Long-Evans rats [10]. Experiments were carried out 3 months latter to STZ injection and those rats having blood glucose level 8-12 mmol/l at fasting condition, were considered to carry out the experiments.

Experimental groups

The experimental animals were divided into four groups as follows:

(i) Normal water control group (n=8): Rats of this group received deionized water at a dose of 10ml/kg bw [11].

(ii) T2DM water control group (n = 7): This group also received deionized water at a dose of 10 ml/kg bw.

(iii) T2DM positive control group (n=8): This group of rats received Glibenclamide at a dose of 5 mg/10 ml (9.9 ml H_2O + 0.1 ml Twin 20)/kg bw [12].

(iv) T2DM treated group (n = 10): This group was administered orally with ethanol extract of *Zingiber officinale* at a dose of 1.25 g/ 10 ml/ kg bw [12].

Rats of all groups were kept under similar environmental conditions, and were provided with enough food and water throughout the experiment. The body weight of each rat was measured in each week.

Chronic study

Each group of rats was fed for 42 consecutive days. An oral glucose tolerance test (OGTT) was performed on the 21st day of the study. The rats were fasted for 12 hours on the 0th, 21st and 42nd day to measure the fasting blood glucose level. Blood samples were collected to measure serum glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum creatinine, SGPT, liver glycogen and serum insulin levels.

Effect on sucrose absorption from gastrointestinal tract

Experiments were carried out on normal rats. Rats were fasted for 12 h before receiving a 50% sucrose solution by gavage (2·5 g/kg body weight) with (for experimental) or without (for control) ethanol extract of *Zingiber officinale* Linn (1·25 g/kg body weight). Blood samples were collected by amputation of the tail tip under mild diethyl ether anesthesia [13]. Blood samples were collected at 30 min before sucrose load and at 30 and 60 min after sucrose administration to determine the glucose level. Finally rats were sacrificed to collect the gastrointestinal tract. The gastrointestinal tract was excised and divided into 6 segments: the stomach, the upper 20 cm, middle, and lower 20 cm of the small intestine, the cecum, and the large intestine. Each segment was washed out with ice-cold saline, acidified with H_2SO_4 and centrifuged at 3000 rpm (1000 g) for 10 min. The supernatant thus obtained was boiled for 2 h to hydrolyze the sucrose and then neutralized with NaOH. The blood glucose level and the amount of glucose liberated from residual sucrose in the gastrointestinal tract were measured. Then the gastrointestinal sucrose content was calculated from the amount of liberated glucose [14]. Glucose was measured by glucose-oxidase (GOD-PAP) method.

Biochemical analysis

Serum glucose was measured by glucose-oxidase method (Sera Pak, USA). The total cholesterol, triglyceride (TG), HDL and LDL by enzymatic-colorimetric method (Randox Laboratories Ltd., UK). Serum insulin by Rat Insulin enzyme linked immunosorbent assay (ELISA) method (Crystal Chem Inc., USA). SGPT was estimated by UV method using ALA (Alanine amino transferase) (GPT) opt. kit (Randox, UK). Estimation of serum creatinine was done by alkaline picrate methods (Randox, UK). Liver glycogen levels were estimated by Anthrone-sulphuric acid method (Vries, 1954). The absorbance was measured by microplate ELISA Reader (Bio-Tek EL-340, USA).

Statistical analysis

Data analysis were done by using the Statistical Package for Social Science(SPSS) software for Windows version 12 (SPSS Inc., Chicago, Illinois, USA). All the data were expressed as Mean ± SD or as Median (Range) as appropriate. Statistical analysis of the results was performed by using the student's t-test (paired and unpaired) or ANOVA (analysis of variance) followed by Bonferroni post hoc test or Mann Whitney (u) test. The limit of significance was set at $p<0.05$.

RESULTS

Effect on the body weight (BW)

Though there was no statistically significant changes in the body weight but there was a tendency to increase in body weight in all groups and the weight gain in normal rats was higher (13%) than the type 2 diabetic rats (2-4%) at the end of study period. (Figure 1)

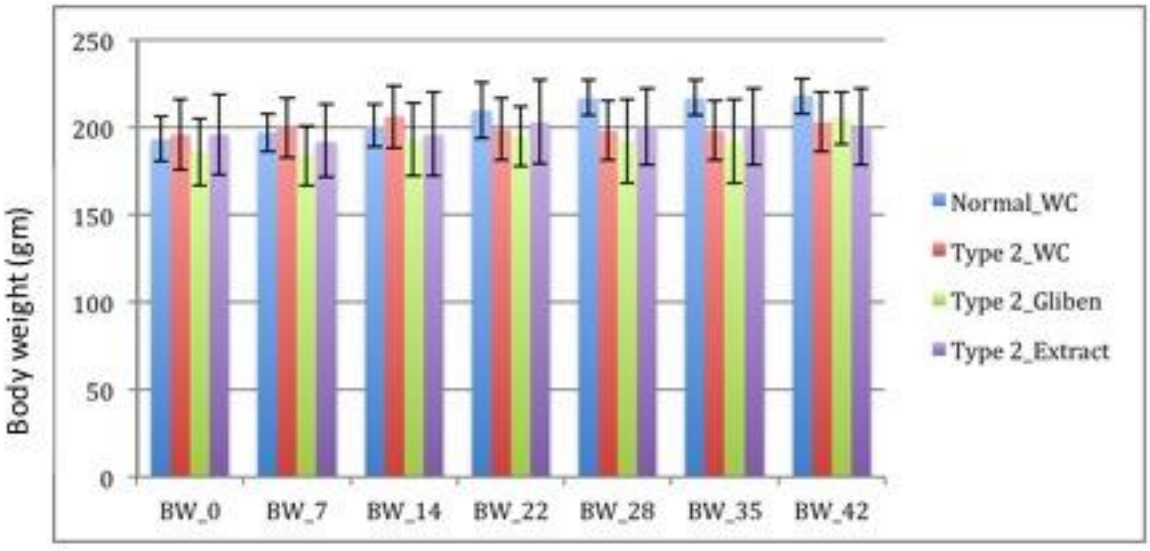

Fig. 1: Chronic effect of *Zingiber officinale* on the body weight of type 2 diabetic model rats.

Data were expressed as Mean ± SD and compared using paired 't' test. BW = Body weight, WC = water control; Gliben = glibenclamide.

Effect of Zingiber officinale on glucose metabolism

Chronic effect of *Z. officinale* on fasting glucose level of type 2 rats is shown in figure 2. In case of normal control rats, no considerable changes were found. On the other hand, feeding of 50% ethanol extract of *Z. officinale* resulted in significant decrease (p=0.002) of fasting serum glucose level on 42 days in comparison to type 2 control rats (serum glucose, M + SD, mmol/l: 6.9 + 1.0 Vs 8.5 + 0.7). Glibenclamide (the positive control) feeding for 21 days significantly decreased (p<0.05) serum glucose level (M + SD, mmol/l, 8.1±1.4 on day 0 Vs 6.3±0.8 on day 21). However, after 42 days of glibenclamide treatment, the serum glucose level was similar to the baseline level of type 2 rats. Serum glucose level was significantly higher (p=0.003) in type 2 control group in comparison to normal control (M + SD, mmol/l, 6.8+ 0.2 in normal control Vs 8.5 + 0.7 in type 2 control).

Chronic effect on blood serum with simultaneous glucose load

To further evaluate the effect of *Z. officinale* on glucose metabolism, we performed oral glucose tolerance test (OGTT) on 22 day of the experimental period. Though statistically it was not significant between the groups but it was found that the percentage of increase of serum glucose at 30 minutes was 28%, 146%, 184% and 177% in normal rats, Type 2 control rats, glibenclamide treated and extract treated groups respectively and at 90 minutes it was 35%, 137%, 180% and 200%, respectively (Figure 3). So, it concludes that oral glucose tolerance status is not improved by *Z. officinale* treatment.

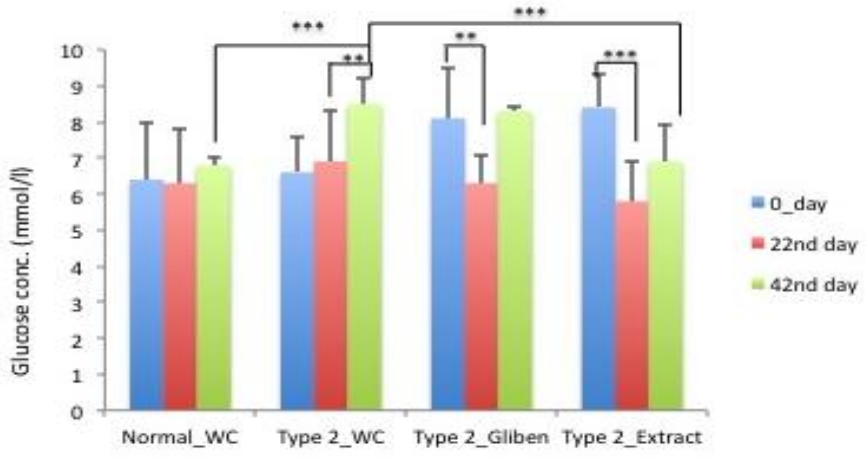

Fig. 2: Chronic effect of *Z. officinale* on the fasting blood glucose levels of type 2 diabetic model rats.

Results were expressed as Mean ± SD; between and within groups, comparison was done using one-way ANOVA with post Hoc Bonferroni test. WC = water control; Glib = glibenclamide; ** p<0.05, ***p = 0.002.

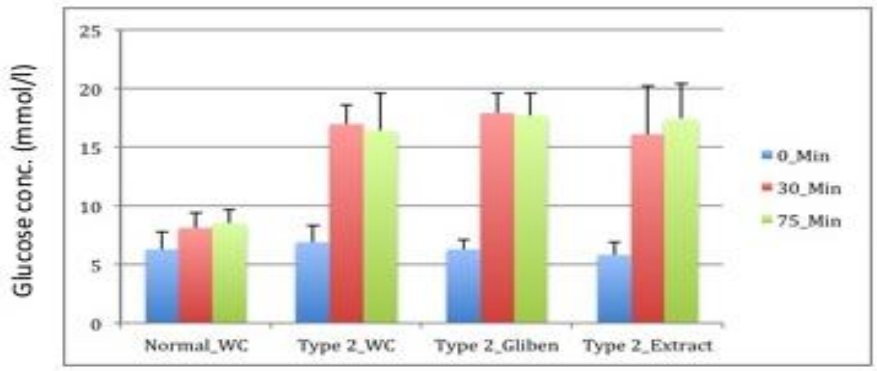

Fig. 3: Effect of *Z. officinale* on postprandial serum glucose levels of type 2 diabetic model rats when fed simultaneously with glucose load on the 22nd day.

Data were expressed as Mean ± SD; between groups comparison was done using one-way ANOVA with post Hoc Bonferroni test. WC = water control; Gliben = glibenclamide.

Effects on lipidemic status

Z. officinale has suppression effect on serum total cholesterol and triglyceride level. It was found that in type 2-control rat there was an increase in cholesterol (6%) and TG (significantly, p<0.01) level in comparison to baseline level. Glibenclamide also significantly increased (p<0.01) the TG level comparing to the baseline value. On the contrary, administration of *Z. officinale* for 6 weeks resulted in a significant decrease (p<0.05) in serum cholesterol level. Serum TG level was also decreased in *Z. officinale* treated group although non-significantly (p=0.073) (Figure 4). Normal control group showed decreased (significantly, p<0.05) TG level. This data clearly showed that total cholesterol level was decreased more effectively by the *Z. officinale* extract rather than glibenclamide and water treated control groups from the initial day and it also supports decreasing tendency of TG.

It was also found that HDL cholesterol level was increased by 3% and LDL cholesterol by 16% in type 2 control rats. Glibenclamide increased the serum HDL-cholesterol by 2%, but decreased (significantly, p<0.05) atherogenic LDL by 50%. Beneficial effect on atherogenic lipids was obtained by chronic administration of *Z. officinale* on type 2 rats. HDL cholesterol was significantly (p<0.05) increased and LDL cholesterol decreased (significantly, p<0.05) by 80% in comparison to baseline level (Figure 4). So, these data elucidates that *Z. officinale* has beneficial effect on atherogenic lipids.

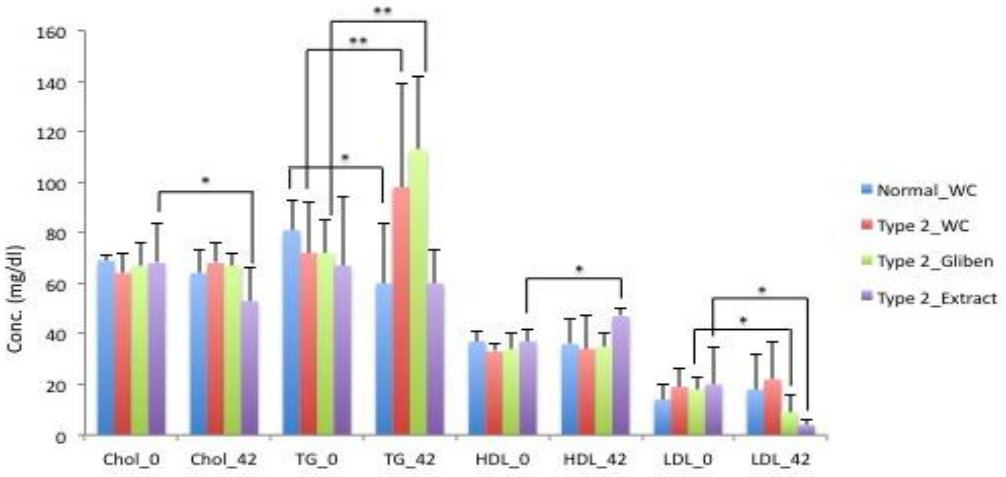

Fig. 4: Chronic effect of ethanol extracts of *Z. officinale* on lipid profile of Type 2 Diabetic Model rats.

Data were expressed as Mean ± SD and compared by paired 't' test. * p<0.05, WC = water control; Gliben = glibenclamide.

Chronic effect of on liver and kidney function

It was observed that in type 2 control rats there was 31% increase in serum ALT level in comparison to baseline level. No significant change was found in serum creatinine levels in case of normal control, type 2 control and glibenclamide treated groups. However, serum creatinine level was decreased significantly after 42 days of consecutive feeding of Z. officinale in comparison to type 2 control groups (p<0.05) (Table 1).

Chronic effect on serum insulin level & hepatic glycogen content

Next we checked the effect of *Z. officinale* on insulin secretion. It is clearly seen from the table that all the groups of Type 2 rats had a significantly lower insulin level on 0 day, in comparison to normal rats. But on the day 42nd, serum insulin level was decreased in normal control group and also in type 2 water treated group. On the contrary, the insulin level for glibenclamide and extract treated groups was significantly increased (p<0.05 and p<0.01 respectively), at the end of study period (Table 2).

Table 1: Chronic effect of *Zingiber officinale* on liver and kidney function

Mean (+ SD)				
Group	**Creatinine (mg/dl) 0 day**	**Creatinine (mg/dl) 42nd day**	**SGPT (mg/dl) 0 day**	**SGPT (mg/dl) 42nd day**
Normal – WC (n = 6)	0.74±0.19	0.48±0.28	57±22	60±13
Type 2 WC (n = 6)	0.84±0.20	0.74±0.14	51±18	67±14
Type 2 Glib (n = 6)	0.78±0.16	0.57±0.26	36±23	33±10
Type 2 Extract (n = 6)	0.88±0.26	0.31±0.27**	54±26	45±15

Results were expressed as Mean ± SD; between groups comparison was done using one-way ANOVA with post Hoc Bonferroni test. WC = water control; Glib = glibenclamide; **p <0.05.

Table 2: Chronic effect of *Zingiber officinale* on the serum Insulin level and hepatic glycogen content of Type 2 Diabetic Model rats

Serum Insulin level (ng/ml) 'Median (Range)'			**Glycogen (mg/g) Mean (+ SD)**
Group	0 day	42nd day	42nd day
Normal-WC (n = 6)	1.344 (0.846-1.739)	1.209 (0.527-3.986)	10.7±5.9
Type 2 WC (n = 5)	0.351 (0.138-0.380)	0.276 (0.101-1.313)	30.0±18.6
Type 2 Glib (n = 5)	0.350 (0.163-0.713)	0.838* (0.563-2.388)	49.4±13.0***
Type 2 Extract **(**n =6)	0.263 (0.136-0.913)	1.101** (0.538-2.787)	40.8±14.1**

Results were expressed as Mean ± SD; between group comparisons was done using Mann -Whitney U test (for serum insulin) and using one-way ANOVA with post Hoc Bonferroni test (for hepatic glycogen). WC = water control; Glib = glibenclamide; *p<0.05, **p<0.01, ***p<0.001.

Hepatic glycogen content of type 2 diabetic model rats was studied after 42 days of chronic feeding (on 42nd day). It was observed from this study that hepatic glycogen content was significantly increased in glibenclamide (p=0.000) and the test groups (p=0.002) after 42 days of oral administration of ethanol extract of *Z. officinale* respectively (Table 2).

Effect on sucrose absorption from gastrointestinal tract

Next, we studied the effect of *Z. officinale* on glucose absorption in different segments of gut. After sucrose loading (2.5 g/kg body weight), the sucrose was detected in different amount in six different parts of the gastrointestinal tract after I hour and 2 hour. The amount of sucrose detected was 18.55 + 10.22 mg in the stomach, 3.65 + 3.88 mg in the upper intestine, 10.35 + 8.07 mg in the middle, 2.17 + 3.98 mg in the lower of the small intestine, 0.10±1.17 mg in the coecum and 1.10±1.94 in the large intestine after 60 min. After 120 min, it was 5.76±6.35 mg in the stomach, 0.69±0.26 mg in the upper, 0.59±0.27 mg in the middle, 1.03±0.65 mg in the lower of the small intestine, 0.83±0.39 mg in the coecum and 0.96±0.50 mg in the large intestine respectively.

Simultaneous administration of 50% ethanol extract of *Z. officinale* increase the content of sucrose in the stomach after 1 hour compared to control. But after 2 hour it was similar in the stomach and upper 20 cm of small intestine. No significant change in the remaining sucrose content was observed between the control and 50% ethanol extract treated group (Figure 5).

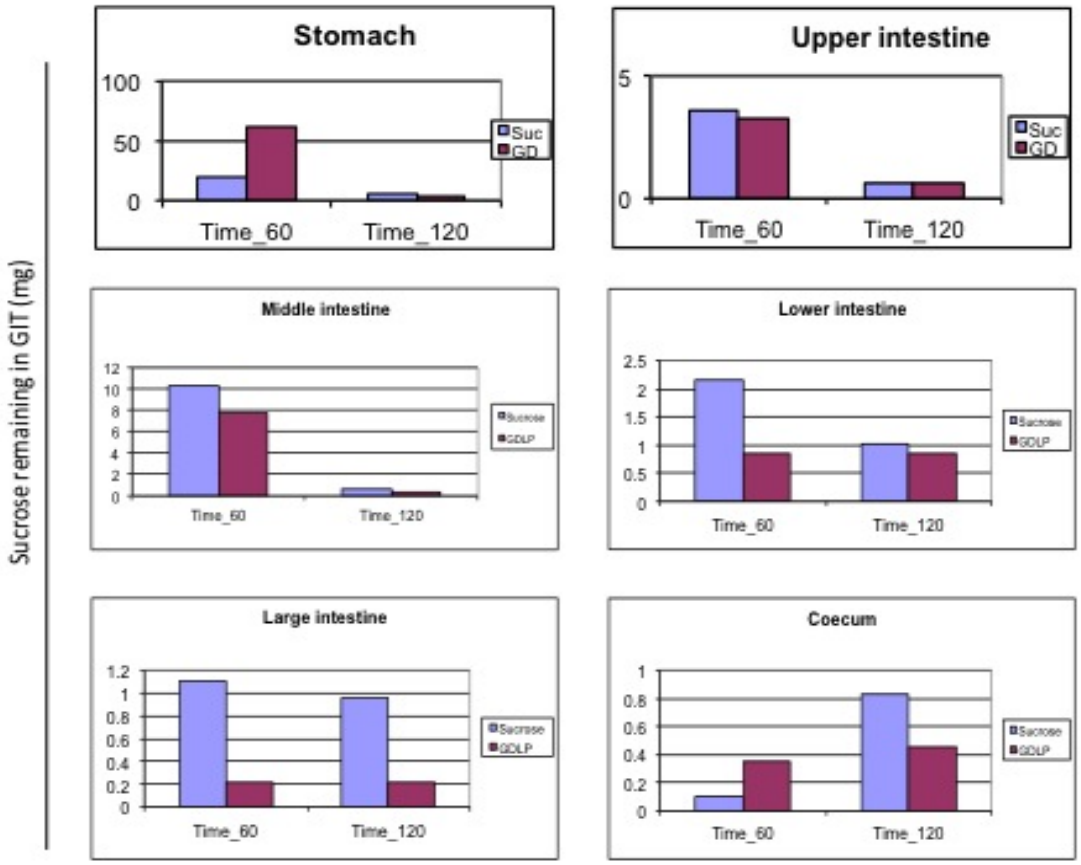

Fig. 5: Amount of sucrose (mg) remained (Mean + SD) in the six different parts of the gut after 60 min and 120 min of oral sucrose loading in normal rats.

Rats were fasted for 20 hours and orally administered a sucrose solution (2.5 g/kg body weight) with or without ethanol extract of *Zingiber officinale*. Results were presented as Mean + SD (n=5 for 60 min, n=3 for 120 min).

DISCUSSION

The effectiveness of *Zingiber officinale* treatment has been reported in alloxan [6] and STZ [15] induced diabetic animals as well as in human subjects [16]. The aim of the present study was to investigate the effect of 50% ethanol extract of *Z. officinale* in serum glucose, serum lipids, serum insulin, serum creatinine, serum alaninamino transferase and liver glycogen contents of type 2 diabetic model rats after chronic administration. Type 2 diabetes develops as a result of insulin resistance in target tissues and impaired insulin secretion, accompanied by increased adiposity. Since this type 2 diabetic model rats used in this study was made by injecting neonates, these model rats of type 2 diabetes did not reduce body weight. Moreover they could gain body weight even with the impairment of insulin secretion, and our study rats gain body weight (although non-significant) throughout the study period. It also indicates that 50% ethanol extract of *Z. officinale* has no effect on degradation of fat depot, which is a common problem in diabetes mellitus.

The present study revealed that 50% ethanol extract of *Z. officinale* produced significant hypoglycemic effect in the fasting state of type 2 diabetic model rats. Our findings are in accordance with other investigators [15, 17]. Significant hypoglycemic effect that was found in the fasting state of type 2 model rats indicated that the blood glucose lowering effect of the ethanol extract of *Z. officinale* is probably due to enhanced insulin releasing activity.

In order to know the probable mechanism of hypoglycemic effect, the serum insulin level of type 2 rats were determined after 42 days of chronic feeding of *Z. officinale.* It was found that type 2 diabetic rats were hypoglycemic in comparison to normal control rats (baseline M + SD, insulin normal control vs. type 2 diabetic control. Treatment for 42 days with ethanol extract of *Z. officinale* increased serum insulin level by 220% in comparison to the baseline level. Although it did not achieve the normal control value, but the rise in insulin content was noticeable. In contrast, type 2 control rats had lower insulin level after 42 days of study period. The obtained results clearly demonstrated that *Z. officinale* has insulin releasing effect. Our results comply with Akhani *et al* [17] who showed that STZ-diabetes produced a significant increase in serum fasting glucose levels that was associated with a significant decrease in serum insulin levels. Treatment with ginger juice produced a significant increase in insulin levels and a decrease in fasting glucose levels in diabetic rats. Moreover in an oral glucose test treatment with ginger juice was found to decrease significantly the area under the curve of insulin in STZ-rats. However, our results do not correlate with this. We did not get improvement in glucose tolerance that was performed on 22 days of feeding of *Z. officinale*. This may be due to the short period of *Z. officinale* treatment.

It has been demonstrated that persistent hypoglycemia is an important cardiovascular risk factors in type 2 diabetic patients [18]. The association of hypoglycemia with an alteration of lipid parameters presents a major risk for cardiovascular complications in diabetes. In addition to glycemic control, treatment of hyperlipidemia also results in significant micro and macrovascular diseases in individuals with type2 diabetes [19]. In the present study, the effects of *Z. officinale* on lipid profiles were evaluated in 42 days chronic feeding experiment. Administration of 50% ethanol

extract of *Z. officinale* lowered serum total cholesterol, triglycerides, harmful LDL-cholesterol and increase atheroprotective HDL-cholesterol level in type 2 diabetic rats. This finding also complies with other investigators [20]. Under normal circumstances, insulin activates the enzyme lipoprotein lipase and hydrolases triglycerides [21]. However in insulin deficient subjects, it fails to activate the enzyme and causes hypertriglyceridemia. The ethanol extract of *Z. officinale* increase insulin production in STZ-hyperglycemic rats, which might lower the triglycerides levels by activation of enzyme lipoprotein lipase.

Liver glycogen level may be considered as the best marker for assessing hypoglycemic activity of any drug. This indicates that peripheral free glucose is being store in the liver in the form of glycogen by increasing glycogenesis. Increased liver glycogen level was observed in 50% ethanol extract of *Z. officinale* treated group in type 2 model rats. Therefore, it may be ascertained that the hypoglycemic activity of *Z. officinale* in type 2 model rats is due to increased uptake of glucose for the formation of glycogen by enhanced glycogenesis. This might be the possible mechanism for the hypoglycemic action, as the extract has no role on the gut sugar absorption. Moreover the ethanol extract of *Z. officinale* has no detrimental effect on liver and kidney functions since no significant change was observed on serum ALT and creatinine level.

It is well known that ginger contains a number of potentially bio-active substances, mainly gingerols and their related dehydration products, the shogaols, as well as volatile oils including sesquiterpenes, such as b-bisabolene and (-)-zingi- berene, and monoterpenes, mainly geranial and neral [22, 23]. In particular, gingerols have been shown to inhibit both prostaglandin and leukotriene biosynthesis [24] and angiogenesis [25]. In addition, several ginger components exhibit serotonin receptor-blocking activity [26]. Gingerol has been identified as an active constituent, which increases insulin sensitive glucose uptake [27]. So, gingerol would be an effective component having antihyperglycemic activity.

CONCLUSION

Our data suggests that *Zingiber officinalie* has hypoglycemic as well as hypolidemic effect, which reflects its anti-diabetic effect, and it is partly mediated by increasing glycogenesis.

ACKNOWLEDGEMENTS

We gratefully acknowledge the financial support of International Program for the Chemical Sciences (IPICS), Uppsala, Sweden, International Foundation for Sciences (IFS), Stockholm, Sweden and Diabetic Association of Bangladesh in conducting this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

REFERENCES

1. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care. 2003; 26: 1277 – 1294.
2. Ravi K, Rajasekaran S, Subramanian S. Antihyperlipidemic effect of *Eugenia jambolana* seed kernel on streptozotocin induced diabetes in rats. Food Chem. Toxic. 2005; 43: 1433 – 1439.
3. Nadkarni MM, Nadkarni AK. Indian Materia Medica. Vol. II. Medicus XLIV, 28–32. Popular Prakasan, Bombay, India, p. 101; 1992.
4. Bhandari U, Ahmed J, Pillai KK. An overview of *Zingiber officinale* (ginger); Chemistry and pharmacological profile. Hamd Med. 2001; 44: 28–32.
5. Sharma M, Shukla S. Hypoglycaemic effect of ginger. J. Res. Indian Yoga Homoeopathy. 1977; 12: 127–130.
6. Ahmed RS, Sharma SB. Biological studies on combined effects of garlic (*Allium sativum* Linn) and ginger (*Zingiber officinale* Roscoe) in albino rats. J Exp. Biol. 1997; 35:841-843.
7. Bhandari U, Grover JK. Effect of ethanolic extract of ginger on hyperglycemic rats. Int. J Diab. 1998; 6:95–96.
8. Fuhrman B, Roseblate M, Hayek T, Coleman R, Aviram M. Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice. J. Nutr. 2000; 130: 1124-1131.
9. Bhandari U, Sharma JN, Zafar R. The protective action of ethanolic ginger (Zingiber officinale) extract in cholesterol-fed rabbits. J. Ethnopharmacol. 1998; 61:167-171.
10. Bonner-Weir S, Trent DF, Honey RN, Weir GC. Responses of neonatal rat islets on srteptozotocin limited beta cell regeneration and hyperglycemia. Diabetes. 1981; 30:64-69.
11. Morshed MA, Haque A, Rokeya B, Ali L. Anti-hyperglycemic and lipid lowering effect of *Terminalia arjuna* bark extract on streptozotocin induced type 2 diabetic model rats. Int. J Pharm. Pharm. Sci. 2011; 3: 449-453.
12. Ali L, Azad Khan AK, Mamun MIR, Mosihuzzaman M, Nahar N, Nur-E-Alam M, Rokeya B. Studies on hypoglycemic effects fruit pulp, seed and whole plant of *Momordica charantia* on normal and diabetic model rats. Planta Medica. 1993; 59: 408-412.
13. Mamun MIR, Rokeya B, Choudhury NS, Muniruzzaman M, Nahar N, Ahmed MU, Mosihuzzaman M, Ali L, Khan AKA, Khan SH. Anti-hyperglycemic effect of *Pterospermum acerifolium* wild and *Pterospermum semisagittatum* ham. Diabetes Res. 2001; 35: 163-170.
14. Goto Y, Yamada K, Ohyama T, Matsuo T, Odaka H, Ikeda H. An alpha-glucosidase inhibitor, AO-128, retards carbohydrate absorption in rats and humans. Diabetes Res Clin Pract. 1995; 28: 81–87.
15. Al-Amin ZM, Thomson M, Al-Qattan KK, Peltonen-Shalaby R, Ali M. Anti-diabetic and hypolipidemic properties of ginger (*Zingiber officinale*) in streptozotocin induced diabetic rats. Br J Nutr. 2006; 96:660–666.
16. Bordia A, Verma SK, Srinvastava KC. Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenumgracecum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids. 1997; 56:379–384.
17. Akhani SP, Vishwakarma SL, Golyal RK. Anti-diabetic activity of *Zingiber officinale* in streptozotocin-induced type I diabetic rats. J Pharm Pharmacol. 2004; 56:101–105.
18. Polisso G, Rijso MR, Barbeieri M, Manzella D, Ragno E, Maugeri D. Cardiovascular risk in type 2 diabetes and pharmacological regulation of mealtime glucose excursions. Diabetes Metab. 2003; 29: 335-340.
19. UK Prospective Diabetes study (UKPDS) Group, Intensive blood-glucose Control with sulphonylurea or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes (UKPDS 33). Lancet. 352:837-53; 1998.
20. Rajasekaran S, Ravi K, Sivgananam K, Subramanian S. Beneficial effects of aloe vera leaf gel extract on lipid profile status in rats with streptozotocin diabetes. Clin Exp Pharmacol Physiol. 2006; 33: 232-237.
21. Nikkilä EA, Taskinen MR, Sane T. Plasma high-density lipoprotein concentration and sub-fraction distribution in relation to triglyceride metabolism. Am Heart J. 1987; 113:543-548.
22. Chevallier A. The Encyclopedia of Medicinal Plants. London. Dorling Kindersley Ltd. 1996.
23. Ursell A. TheComplete Guide to Healing Foods. London: Dorling Kindersley Ltd. pp.112 – 114; 2000.
24. Kiuchi F, Iwakami S, Shibuya M, Hanaoka F, Sankawa U. Inhibition of prostaglandin and leukotriene biosynthesis by gingerolsanddiarylheptanoids.ChemPharm Bull. 1992; 40:387 – 391.
25. Kim EC, Min JK, Kim TY, Lee SJ, Yang HO, Han S, Kim YM, Kwon YG. Gingerol, a pungent ingredient of ginger inhibits angiogenesis in vitro and in vivo. Biochem Biophys Res Comm. 2005; 335: 300–308.
26. Huang QR, Iwanmoto M, Aoki S, Tanaka N, Tajima K, Yamahara J, Takaishi Y, Yoshida M, Tomimatsu T, Tamai Y. Anti-5-hydroxytryptamine-3 effect of galanolactone, diterpenoid isolated from ginger. Chem Pharm Bull. 1991; 39: 397–399.
27. Sekiya K, Ohtani A, Kusano S. Enhancement of insulin sensitivity in adipocytes by ginger. Biofactors. 2004; 22:153-156.