Guggul Resin Extract Improve hyperglycemia and Lipid Profile in Streptozotocin Induced Diabetes Mellitus in rats

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Abstract: Natural products is an affective approach for the treatment of diabetes and prevention of associated complications. The objective of the current study is to explore the potential impact of guggul resin aqueous extract (GRE) obtained from *Commiphora mukul* against hyperglycemia and associated metabolic disorders in streptozotocin (STZ) induced diabetes in rats. The results showed that oral administration of GRE (40 mg/kg body weight) to diabetic rats effectively reduced the elevated plasma glucose and glycosylated hemoglobin (HbA1c) levels and up-modulated the decrease in C-peptide and insulin levels compared to normal rats. The plant extract also successfully reduced the elevated plasma lipids including triglycerides (TG), total cholesterol (TC) and low density lipoprotein (LDL-C) and modulated the decrease in the high density lipoprotein (HDL-C), and the associated hypertension in diabetic rats versus normal ones. The result also showed that the plant extract was effective in ameliorated plasma adeponectin of diabetic rats versus normal ones. Plasma homocysteine was lowered in diabetic animals compared to control ones, however, non significant change in its level was observed between diabetic animals and diabetic-GRE treated group. In conclusion, the present study proved that GRE has good glycemic control which may related to its antioxidant potential action, hence with its antioxidant activity, treatment with this plant extract can be effective in treatment of diabetes and associated disorders.
[Widad M. Al- Bishri and Omar S. Al-Attas. **Guggul Resin Extract Improve hyperglycemia and Lipid Profile in Streptozotocin Induced Diabetes Mellitus in rats.** *Life Sci J* 2013;10(1):2735-2741] (ISSN:1097-8135). http://www.lifesciencesite.com. 327

Keywords: *Commiphora mukul*, diabetes, metabolic disorders, adeponectin

1. Introduction

Diabetes mellitus is a serious, complex chronic condition which is a major source of ill health all over the world. This metabolic disorder affects approximately 4% of the population worldwide and is expected to increase by 5.4% in 2025 (**Kim *et al.*, 2006**). Diabetes mellitus is a disease due to abnormality of carbohydrate metabolism and characterized by absolute (type I) or relative (type II) deficiencies in insulin secretion or receptor insensitivity to endogenous insulin, resulting in hyperglycemia (**Alberti and Zimmet, 1998).** It is well proved that chronic hyperglycemia is associated with long-term damage, dysfunction and finally organs failure including heart, kidney, eyes and blood vessels (**Susheela *et al.*,2008).** In addition, some studies have demonstrated a relationship between chronic complications and duration of diabetes, hypertension, and dyslipidemia (**Bain *et al.*, 2000**). Plasma C-peptide concentrations provide an indirect measure of the insulin secretory reserve (**Polonsky *et al.*, 1995**). The relationship between blood C-peptide level and chronic diabetic complications was also investigated in clinical study (**Sari and Balci, 2005**). The authors reported that serum C-peptide level was higher in diabetic patients with dyslipidemia, hypertension, coronary artery diseases(**Sari and Balci, 2005**). Also, other authors reported an increased in the amino-acid, homocysteine, level in plasma of diabetic patients with hypertension as an important risk factor for vascular disease, including coronary atherosclerosis (**Tarkun *et al.*, 2003).** An another disorder induced in response to diabetes related to adiposity, is the decrease in adeponectin level which has an important role in insulin-sensitizing effect (**Scherer *et al.*,1995**) . Reduction of adiponectin has been associated with insulin resistance, dyslipidemia, and atherosclerosis in humans **(Yadav *et al.*,2013**).

The current treatment although provide good glycemic control but do a little in preventing complications. Besides, these drugs are associated with side effects **(Berger, 1985).** Moreover, providing modern medical healthcare across the world is still a far-reaching goal due to economic constraints. Thus, it is necessary that we continue to look for new and more effective drugs and the vast reserves of phytotherapy may be an ideal target. In any form of management of diabetes with insulin or drug, diet is a common factor.

With respect to diet, plants and foods of medicinal value have proved to be very useful and are in wide usage as they combine two basic central factors: food and medication **(Grower *et al.*,2002).**

The genus *Commiphora* (Burseraceae) has different species distributed in the tropical and subtropical regions (**Vollesen, 1989; Langenheim, 2003).** The plant species are characterized as small trees or shrubs with pine- scent branches, pale-gray bark and reddish-brown resinous exudates. The resinous exudates of the genus *Commiphora* are used as perfume and Incense beside the well known its medicinal values (**Langenheim, 2003).** They are used in medicines for the treatment of wound, pain, arthritis, fractures, obesity, parasitic infection and gastrointestinal diseases **(Al-Harbi *et al.*, 1997; Abdul-Ghani *et al.*, 2009; Zhang, 2009).** Diverse secondary metabolites including terpenoids, steroids, flavonoids, sugars, lignans, etc. have been discovered in this genus **(Hanuˇs *et al.*, 2005).** Antiproliferative, anti-inflammatory, antimicrobial, hepatoprotective and cardiovascular properties of the purified metabolites and the crude extracts have been investigated (**El Ashryetal., 2003; Deng, 2007; Shen and Lou, 2008; Ramesh *et al.*, 2012).** *Commiphora mukul* is one of the **Commiphora species.** Oleogum resin extract (known as guggul or gum guggul) obtained from *Commiphora mukul* has been used for a wide variety of ailments, including atherosclerosis, hypercholesterolemia, rheumatism, obesity, diabetes,cardiovascular diseases and hypothyroidism (**Panda and Kar, 2005; Deng, 2007; Bellamkonda *et al.*,2011)** as well as anti-inflammatory potential action (**Bellamkonda *et al.*, 2011, Ojha *et al.*,2011).** Recent studies have also indicated that guggulsterones improve insulin production by protecting pancreatic beta cells **(Lv *et al.*, 2008)**.

The objective of the current study is to investigate the beneficial effects of aqueous extract of *commiphora mukul* resin on biomarkers of glycemic control, hyperlipidemia and insulin sensitivity in STZ induced DM in Wister albino rats.

2.Material and Methods

Chemicals:

All chemicals used were of high analytical grade, product of Sigma and Merck companies. Kits used for the quantitative determination of different parameters were purchased from Biogamma, Stanbio, West Germany.

Animals

The current study was conducted in accordance with the guidelines set by the ethical committee, College of Science Research Center, King Abdulaziz University, Jeddah, Saudi Arabia. Male Wister albino rats of 8 weeks old, weighing 150-170 g were obtained from the College of Pharmaceutical Sciences and left to acclimatize to the environmental conditions of animal facility for two weeks under a 12 h light-dark cycle and at 22±3°C temperature. Rats were provided with water and normal standard diet *ad libitum*.

Preparation of resin aqueous extract

Guggul resin was obtained locally. 10 g of the resin was soaked in 100 ml of boiled water for 8 hours at room temperature to prepare the aqueous extract of guggul resin. The soaked content filtered, then the filtrate was stored in dark bottles to be used within 3 days.

Experimental design

Rats were divided into three groups, each of 8 rats
Group 1: Normal healthy rats
Group 2: Diabetic rats
Group 3: Diabetic rats treated with guggul resin aqueous extract (GRE)

Diabetes was induced by STZ, each rat was injected intraperitoneally with a single dose of STZ (40 mg/Kg body weight) dissolved in 0.01M citrate buffer (pH 4.5) immediately before use. After injection, they had free access to food and water and were given 5% glucose solution to drink overnight to counter hypoglycemic shock (**Bhandari *et al.*, 2005).** After three days, diabetic status of the rats was evaluated by measuring the plasma glucose levels. Hyperglycemic rats (> 250 mg/dL) were used for the experiment. GRE was given to rats orally (1 ml /100 g body weight) daily for 8 weeks commenced 4 days after induction of diabetes.

Sample collection

Three days after the induction of diabetes in STZ group animals, blood samples were collected from retro orbital plexus from the rats of all the groups. These blood samples served to provide the base line values (time=0) for all the studied parameters. After 4 weeks and at the end of 8 week treatment duration, the animals were fasted overnight (12-14 hours), the blood samples were collected from each animal in all groups into sterilized tubes containing heparin for plasma separation. Plasma was separated by centrifugation at 3000× g for 10 minutes and stored at -80^{o}C until biochemical analysis.

Biochemical measurements

Fasting plasma **glucose**, **TG** and **TC** were measured using standard enzymatic methods and a fully automated analyzer (Konelab instruments, Finland). **HDL-C** level was determined by phosphotungstic acid/magnesium chloride precipitation (Kone instruments, Finland). **LDL-C** was calculated using Friedewald equation. Atherogenic index of plasma (AIP) was calculated as [cholesterol level – HDL level]/ HDL level. **HbA1c** was measured by HPLC using protein pack using 7.5 x 75 mm SP 5PW column (Waters. France).Plasma samples were treated

with tributyl-N-phosphine to reduce the thiols and deproteinization was done using 10% trichloroacetic acid. The reduced thiols were derivatized with SBD-F (ammonium 7-fluorobenzo-2-oxo-1, 3-dizole-4-sulphonate), thiol-specific fluorogenic probe. Isocratic HPLC using HichromC18, 250x4.6 mm column as the stationary phase and 0.1 M KH2PO4 buffer: acetonitrile mixture in the ratio of 96:4 as mobile phase was employed for the resolution of thiols. The fluorescence detector was set at Ex 385 nm/Em 515 nm to detect the peak of interest. **Insulin** was measured using a solid phase enzyme amplified sensitivity immunoassay (Medgenix INS-ELISA, Biosource, Belgium). Plasma **C-peptide** was evaluated by ELISA method (ALPCO Diagnostics, Salem, NH, USA). Plasma **adiponectin** levels were estimated by radioimmunoassay method following the manufacturer's guidelines. (Linco Research, St Charles, MO, USA). Total plasma **Hcy** was determined by ELISA competitive binding assay using HCYS Flex reagent cartridge on Dimension Vista system (Siemens Health Care Diagnostics Products GmbH, Marburg, Germany). Sample handling and reagent preparations were done according to the manufacturer's instructions.

Statistical analysis

SPSS statistical software was utilized for data analysis. Data represented by Mean ± standard deviation. Assumptions of normality and homogeneity of variance were checked. Square root or Log transformation was done for skewed data. Analysis of Variance (ANOVA) is done among groups of treatments for various parameters followed by Bonferroni. Level of significance was given at $P \leq 0.05$.

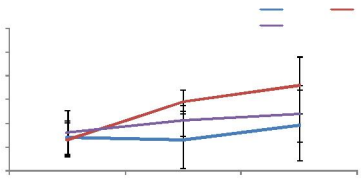

Fig 1 : Effect of GRE treatment on plasma glucose level of diabetic rats after 4 and 8 weeks. Values are expressed as mean ± SD of 3 independent experiments.

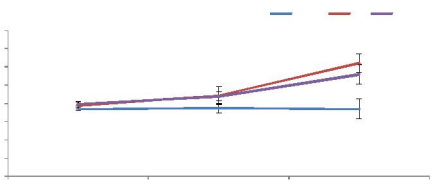

Fig 2: Effect of GRE treatment on the percent of plasma HbA1C of diabetic rats after 4 and 8 weeks . Values are expressed as mean ± SD of 3 independent experiments.

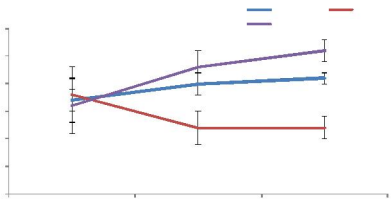

Fig 3: Effect of GRE treatment on the level of plasma Insulin of diabetic rats after 4 and 8 weeks . Values are expressed as mean ± SD of 3 independent experiments

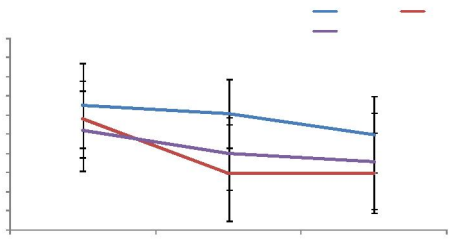

Fig 4: Effect of GRE treatment on the level of plasma C-Peptide of diabetic rats after 4 and 8 weeks . Values are expressed as mean ± SD of 3 independent experiments.

3.Result

The plasma glucose, HbA1c, C-peptide and insulin levels in normal and diabetic animals as biomarkers of glycemic control are depicted in Figures 1,2,3 and 4 respectively. The results revealed that induction of diabetes to rats led to marked elevated levels of glucose and HbA1c with concomitant reduced levels of C-peptide and insulin compared with normal animals. Oral ingestion of GRE to diabetic rats, effectively ameliorated the alteration in these biomarkers compared with diabetic untreated ones. Table 1 shows the plasma lipid profiles in normal and diabetic animals as biomarkers metabolic disorder in lipid metabolism. From the data, it can be observed elevated levels of TG, TC and LDL-C were elevated in plasma of diabetic rats accompanied with a decrease in HDL-C versus normal rats. The abnormalities in these lipid profiles were associated with increase in TC/HDL and LDL/HDL ratios as well as in atherogenic index (Table 2) in diabetic rats in relation to control ones. Administration of the plant extract, markedly ameliorated the alteration in lipid profiles and the related alteration in the ratios of atherosclerosis indices compared to diabetic untreated group. The result also showed that the plant extract was effective in ameliorated plasma adeponectin of diabetic rats versus normal ones (Figure 5). The result also showed that plasma homocysteine (Figure 6) was lowered in

diabetic animals compared to control ones, however, non significant change in its level was observed between diabetic animals and diabetic-GRE treated group.

Table 1: Blood pressure and lipid profile in control and diabetic rats before and after GRE treatments

		Control	STZ	STZ+GRE	*P* value
N		8	8	8	
TC (mmol/l)	Baseline	1.1±0.10	1.6±0.13*	1.8±0.16*	<0.001
	4 weeks	1.2±0.13	1.7±0.14*	1.6±0.15#	<0.001
	8 weeks	1.2±0.12	1.7±0.12*	1.4±0.25#	<0.01
TG (mmol/l)	Baseline	0.28±0.04	0.49±0.07*	0.50±0.08*	<0.001
	4 weeks	0.28±0.09	0.51±0.08*	0.42±0.07#	<0.001
	8 weeks	0.29±0.03	0.51±0.06*	0.30±0.02#	<0.01
HDL-C (mmol/l)	Baseline	0.68±0.07	0.39±0.05*	0.39±0.07*	<0.001
	4 weeks	0.66±0.05	0.38±0.06*	0.48±0.08#	<0.001
	8 weeks	0.66±0.06	0.40±0.04*	0.60±0.08#	<0.01
LDL-C (mmol/l)	Baseline	0.23±0.04	0.33±0.05*	0.37±0.08*	<0.001
	4 weeks	0.25±0.06	0.36±0.07*	0.31±0.04#	<0.001
	8 weeks	0.25±0.05	0.35±0.06*	0.27±0.04#	<0.01

Lipid profile was compared between normal control and diabetic rats (STZ) at base line (72 h post STZ administration) and at 4 and 8 weeks thereafter. GRE treated diabetic rats were compared with the untreated diabetic rats at base line (72 h post STZ administration) and at 4 and 8 weeks thereafter. Data represented by mean ± SD of 3 independent experiments; '*' represents group is significantly different from Control; '#' indicates group is significantly different from STZ. STZ: streptozotocin, GRE: guggul resin extract, TG: triacylglycerol, TC: total cholesterol, LDL-C: low density lipoprotein, HDL-C: high density lipoprotein.

Table 2: Ratios of atherosclerosis indices in normal and STZ treated groups.

		Control	STZ	STZ+GRE	*P* value
TC/HDL ratio		8	8	8	
	Baseline	1.62±0.17	4.1±0.18*	4.6±0.11#	<0.001
	4 weeks	1.8±0.09	4.4 ±0.1*	3.3±0.11#	<0.001
	8 weeks	1.8±0.09	4.3±0.085*	2.3±0.16#	
LDL/HDL ratio					<0.001
	Baseline	0.33±0.055	0.84±0.05*	0.94±0.075#	<0.001
	4 weeks	0.38±0.045	0.94±0.065*	0.64±0.06#	<0.001
	8 weeks	0.38±0.055	0.90± 0.055*	0.45±0.06#	<0.001
Atherogenic index					
	Baseline	0.62±0.03	3.1±0.08*	3.6±0.09 #	<0.001
	4 weeks	0.81±0.06	3.5±0.1*	2.3±0.08#	<0.001
	8 weeks	0.8 ± 0.06	3.3±0.05*	1.3±0.17#	<0.001

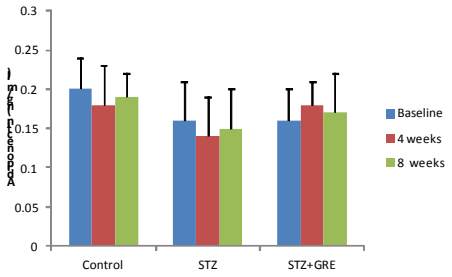

Fig 5: Effect of GRE treatment on the concentration of adeponectin in plasma of diabetic rats after 4 and 8 weeks**.** Values are expressed as mean ± SD of 3 independent experiments.

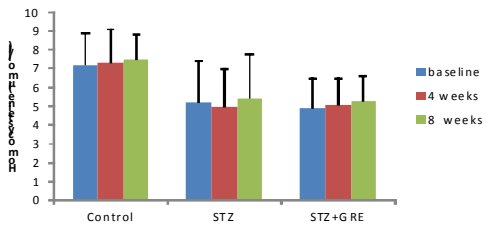

Fig 6: Effect of GRE treatment on the level of plasma homocysteine of diabetic rats after 4 and 8 weeks **.** Values are expressed as mean ± SD of 3 independent experiments.

Result was compared between normal control and diabetic rats (STZ) at base line (72 h post STZ administration) and at 4 and 8 weeks thereafter. GRE treated diabetic rats were compared with the untreated diabetic rats at base line (72 h post STZ administration) and at 4 and 8 weeks thereafter. Data

represented by mean ± SD of 3 independent experiments; '*' represents group is significantly different from Control; '#' indicates group is significantly different from STZ. STZ-streptozotocin, GRE- guggul resin extract, TG-triacylglycerol.

4. Discussion

Little scientific evidence exists to support the numerous herbs used to improve diabetes-related metabolic disorders. It is known that considerable medical resources have been invested on the prevention and control of the diabetes-related complications (**Mohamed *et al.*, 2009).**

The present study showed that injection of rats with STZ resulted in a significant elevation in blood glucose in diabetic control group as compared with normal animals indicating establishment of diabetic state. Hyperglycemia induced by STZ may be resulted from an increased synthesis, secretion or reduced cellular uptake in an insulin depleted environment due to pancreatic beta cell destruction. It was reported that STZ induced diabetes by destroying pancreatic beta cells through generating excessive reactive oxygen species (ROS) which led to lipid peroxidation and DNA damage in pancreatic beta cell **(Lenzen, 2008**). Increased ROS in diabetes can lead to serious complications, including cardiovascular diseases, liver and kidney failure, blindness and nerve injury (**Neyenwe *et al.*,2011**). Previous reports stated that diabetes is developed due to obstruction of glucose utilization by the tissues through glycolysis and its over-production through excessive hepatic gluconeogenesis (**Klover and Mooney, 2004)**.

Oral administration of GRE to diabetic animals markedly down regulated the blood glucose level. Indicating its potential hypoglycemic action. This is consistent with the finding of **Bellamkonda *et al.* (2011).** The hypoglycemic effect of the used extract may be related to the antioxidant effect of its phyto-constituents which have beneficial ability to protect pancreatic beta cells from ROS induced by STZ. This finding is supported by some authors who reported that guggulsterones improve insulin production by protecting pancreatic beta cells **(Lv *et al.*, 2008)**.

Level of glycosylated hemoglobin (HbA1c) is an accepted indicator of glycaemic control of diabetes mellitus. The current study revealed that an increased level of plasma HbA1c in diabetic rats versus normal rats, confirming the hyperglycemic state and impaired glucose metabolism in the STZ treated rats **(Tan *et al.*, 2011)**. Ingestion of GRE significantly reduced HbA1c level compared with diabetic ones. This result may ensure the glycemic control of the used plant extract (**Bellamkonda *et al.*, 2011).**

Plasma C-peptide concentrations provide an indirect measure of the insulin production (**Polonsky, 1995**). In line with previous study,The current study revealed that hyperglycemic state was corroborated with lower plasma insulin and C-peptide, which is a pro insulin molecule and its reduced levels are suggestive of hampered insulin production in response to destruction of most pancreatic beta cells induced by STZ (**Lee and Kang , 2013)**. Oral administration of GRE to diabetic animals markedly up regulated insulin and C-peptide levels indicating its antioxidant potential effect in protecting pancreatic beta cells from oxidative damage by ROS, and turn led to increased insulin production

Elevated lipid profile levels in response to alteration in lipid metabolism, is known to be one of the factors associated with uncontrolled diabetes mellitus. Glucolipotoxicity, which is exerted by high lipids and prolonged hyperglycemia, is implicated in pancreatic β-cell failure in diabetes **(Han *et al.*,2013).** Several studies had indicated significant relationship between glycemicc control of diabetes mellitus with high lipid level (**Raman *et al.*,2012)**. The current study showed induction of diabetes to rats was associated with elevated plasma levels of TG, TC and LDL-C (hyperlipidemia) with concomitant decreased level of HDL-C. in relation to control ones. Alteration in these lipid profiles was reflected by increased atherosclerosis indices in diabetic rats versus control animals. It was found positive correlations between hypertriglyceridemia and hyperglycemia induced by daibetes. Diabetic state induces oxidative stress and reactive oxygen species (ROS) production which reported to have specific roles in the modulation of cellular events (**Stephens *et al.*, 2006)**. ROS react with protein thiol moieties to produce a variety of sulfur oxidations, thus diminishing the insulin receptor signal and inhibiting cellular uptake of triacylglycerol from the blood (**Chen *et al.*, 2003**). Hyperlipidemia which represented by hypertriglyceridemia identified a high risk dysmetabolic situation (**Blackburn *et al.*, 2003**). Some studies have linked hypertriglyceridemia to higher blood small dense LDL particles, atherothrombosis and impaired endothelial function, the hallmarks of several prevalent cardiovascular diseases as well as their complications (**Lundman *et al.*, 2001; Ginsberg, 2002**).

Hypercholesterolemia and abnormalities in lipoprotein metabolism are considered other serious risk factors and important early events in the pathogenesis of atherosclerosis in both peripheral and coronary circulation (**Paez and Gomez, 2009**). Lipid compounds and products of their oxidation especially LDL accumulate during formation of atherosclerotic lesions (**Mallika *et al.*, 2007**). LDL functions in the atheroma formation whereas the HDL plays an important role in inhibiting the formation of atheroma, (**Mallika *et al.*, 2007**). The antiatherosclerotic action of HDL consists in its ability to remove cholesterol

from vascular wall, stimulate prostacyclin formation and inhibit the synthesis of adhesive molecules (**Pal, 2009**). Lowering the plasma lipid levels through dietary or drug therapy may be beneficial in decreasing the risk of vascular disease.

Administration of GRE to diabetic animals significantly down modulated the blood lipid profiles compared with diabetic animals. This result may indicate that the extract contains active compounds with hypo-lipidemic potential action. The beneficial hypolipidemic impact of the used extract was previously documented in diabetic animals under the effect high fructose diet (**Ramesh and Saralakumari**, **2012**). The hypolipidemic impact of the used plant extract may be beneficial in reducing the cardiovascular disease related to diabetic state.

Adiponectin is hormone secreted by human adipose tissue that regulates energy homeostasis and glucose and lipid metabolism **(Ouchi and Walsh, 2008)**. It has an important role in insulin-sensitizing effect (**Scherer *et al.*, 1995**) through enhancing the ability of sub-physiological concentrations of insulin to inhibit gluconeogenesis in hepatocytes (**Wang *et al.*, 2002**). However, it was reported that adiponectin expression decreases with the diabetes and increase in the dyslipidemia (**Scherer *et al.*, 1995**). The current work demonstrated that hyperglycemia induced by STZ in animals was associated with a decrease in adeponectin level. The reduction of adiponectin may be related to diabetic dyslipidemia **(Yadav *et al.*, 2013**). Our result is supported by Clinical study illustrated that low adiponectin was associated with diabetes among diabetic patients (**Kim *et al.*,2013)**. Ingestion of GRE to diabetic animals markedly ameliorated the plasma level of adiponectin versus diabetic untreated counterparts. This potential effect of the used extract may be related to its beneficial roles in mitigating glucolipotoxicity induced in response to diabetic state.

Homocysteine is a non-protein amino acid and is linked to cardiovascular complications. Decreased homocysteine level in the diabetic rats compared to normal ones presented in the current study is in accordance with the previous reports (**House *et al.*,1999).** Oral supplementation of GRE to diabetic rats, showed non significant change in homocysteine level compared with diabetic animals.

In conclusion, the current study proved that GRE has good glycemic control and beneficial in protecting pancreatic beta cells from STZ damaging effect. This good effect of the used plant extract may related to the antioxidant capacity of its active constituent . Hence, with its antioxidant feature, treatment with this plant extract can be effective in treatment of diabetes and associated disorders and may candidate as natural antidiabetic drugs.

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2/20/2013