ORIGINAL ARTICLE

Anti-Hyperglycemic and Anti-Dyslipidemic Activities of Glycyrrhiza Glabra Root Extract In Diabetic Rats

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ABSTRACT

Objective: To compare the anti-hyperglycemic and anti hyperlipidemic activities of ethanolic extract of Glycyrrhiza glabra (licorice) roots with the standard drugs metformin and glimepiride in streptozotocin induced diabetic rats.

Study Design: Experimental study.

Place and Duration of Study: Animal House of Basic Medical Science Institute (BMSI). Jinnah post graduate medical center (JPMC), Karachi conducted from May 2018 till August 2018.

Materials and Methods: Total seven groups of Wistar albino rats comprising six rats in each were included. Study included negative control and positive control groups, to which 0.9% of sodium chloride was administered. Other five groups of streptozotocin induced diabetic rats were treated with metformin, glimepiride, rosuvastatin, ethanolic extract of Glycyrrhiza glabra (licorice) roots at a dose of 200 mg/kg and 400mg/kg, respectively. The treatment was given for 28 days followed by the laboratory estimation of fasting blood glucose (FBG), fasting serum insulin, Glycosylated Hemoglobin A1c (HbA1c), total lipid profile and serum amylase were evaluated.

Results: A significant decrease was observed in all the glycemic indices at both doses of Glycyrrhiza glabra (licorice) i.e. 200 mg/kg and 400mg/kg, but a more rampant decrease is observed at the dose of 400mg/kg. Similarly, both concentrations of extract showed significant decrease in all lipidemic indices that included HDL-C, VLDL-C, LDL-C, total cholesterol (TC), Triglycerides (TG) and the serum amylase levels.

Conclusion: This study concludes that the licorice herb has sufficient anti hyperglycemic and anti hyperlipidemic effects in diabetic rats without any aberration in pancreatic enzymes, hence it might be beneficial as additional dietary supplements for the effective management of diabetes mellitus along with standard drugs.

Key Words: *Diabetes Mellitus, Hyperglycemia, Hyperlipidemia, Licorice.*

Introduction

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia along with weakened metabolism of carbohydrate and other essential energy yielding fuels, such as lipids and proteins."[1] Recently, the International Diabetes Federation (IDF) has reported that around 415 million people were having diabetes mellitus in 2015 and this figure is assumed to raise up to 642 million by 2040 throughout the world.[2] This alarming illness is mainly of two types i.e. type 1 which is caused by relative insulin deficiency while type 2 is mainly attributed to insulin resistance.[3] Along with other co-morbidities, dyslipidemia is also associated with poorly controlled diabetes mellitus which can lead to multiple micro and macro vasculopathies including coronary heart disease and stroke that explains early mortalities and morbidities in diabetic patients.[1]

The oral treatment regimen for diabetes mellitus is classified in to insulin sensitizers, insulin secretagogues and miscellaneous group.[4] The management and control of diabetes by these synthetic drugs without adverse effects is a great challenge because mostly all these oral anti hyper glycemic medications have various distressing complications with development of resistance on enduring exploitation.[5,6] Furthermore, conventionally used most oral hypoglycemic drugs have more side effects on which is the awful

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outcome of poorly controlled diabetes.[7] Herbal drugs remain the focus of attraction by the researchers not only in ancient times but still today a large number of World's population believes that herbal medications are sole remedies for a range of diseases.[8] There are about 45000 plants which possess different medicinal properties including anti hyperglycemic and anti-dyslipidemic activities. G.glabra is the root of Glycyrrhiza inflates (Fabaceae) which is commonly known as sweet wood or licorice. It is regularly used herb for culinary and ayurvedic purposes in South Asia since long time.[9,12] According to current literature, G.glabra is medically used for multiple purposes such an antioxidant, antidote for peptic ulcers and gastritis and prevention as well as treatment of common cold.[13] Furthermore, it has potent anti-tussive activity, muscle relaxing property, weight reduction potential, immune boosting action via increasing WBC counts and anti-diuretic and anti-inflammatory effects.[14] The naturally active constituents of G.glabra are glycyrrhizin, liquiritins, liquiritigenin, glycyrrhizin acids and flavones. Glycyrrhizin is the major saponin in licorice root and its metabolite glycyrrhetinic acid is main pharmacologically active form.[15] Together these flavonoids confirm significant anticancer, antioxidative, antimicrobial, and antiviral effects.[16] Moreover, licorice also reduces the liver damage significantly owing to its antioxidant and anti-inflammatory properties as indicated by Chen et al. in 2014.[17]

However, none of the studies mentioned above have aimed to find out the antidyslipidemic properties of G.glabra. Therefore, in our study we have used G.glabra on rats to find out its effects on the different lipidemic parameters. Moreover, we also aimed to find out the effect of different doses of G. glabra on the lipidemic parameters. Therefore, this study was conducted to compare the anti-hyperglycemic and anti hyperlipidemic activities of ethanolic extract of Glycyrrhiza glabra (licorice) roots with the standard drugs metformin and glimepiride in streptozotocin induced diabetic rats.

Materials and Methods

This was an experimental study conducted between May 2018 till August 2018 in Animal House of Basic Medical Science Institute (BMSI), Jinnah post graduate medical center (JPMC), Karachi. G.glabra root was obtained from the local market of Karachi. The plants were authenticated and identified from botany department of Karachi University and taxonomy number was obtained. (Taxonomic number of Glycyrrhiza glabra i.e. Licorice is: 17234) The study was approved from Ziauddin University.

The G.glabra roots were washed and dried separately in open air for 48 hours. The roots were then minced into powder using a mechanical grinder. The powder was then mixed and infused with absolute ethanol at a 1:10 ratio (100 gram in 1 L solvent) for 7 days in separate jars. The extract was filtered through a Whatman No 1 filter paper which was followed by rotory evaporation of fíltrate with the help of rotary evaporators so that the concentrated extract of herb was obtained which was free of ethanol. The crude extract was reconstituted in freshly prepared 2.5% dimethyl sulfoxide DMSO and kept in jar for evaluation of anti-hyperglycemic and anti-dyslipidemic properties in diabetic rats.

Forty-two adult male and female Wistar albino rats (aged 7-8 weeks, weighing 180–240 grams) were purchased from the animal house of Agha khan university hospital. However, it was made sure none of the rats purchased suffered from any other comorbidity that could have affected our results. All rats were kept in (25 ± 3 C, 12 h light/dark cycle) as well as the standard diet and clean tap water the rats were provided. Rats were divided in 7 groups: Group-I negative control non diabetic rats; treated with 0.9% sodium chloride (NaCl). Group II positive control diabetic rats; treated with 0.9% NaCl. Group-III diabetic rats and was treated with glimepiride at 0.1 mg/kg bw. Group-IV diabetic rats and was treated with metformin at 10 mg/kg bw. Group V diabetic rats; treated with rosuvastatin 10 mg/kg/day bw. Group- VI diabetic rats; treated with Ethanolic Extract of G.glabra at a dose of 200 mg/kg .Group- VII diabetic rats; treated with Ethanolic Extract of G.glabra at a dose of 400 mg/kg.

With the exception of negative control group, diabetes was induced to all animals by injecting the solution of Streptozotocin (STZ). The solution was made by dissolving dry powder of STZ in 0.1 M citrate buffer (pH 4.5) that was used after filtration.[17] It was injected as a single dose of 55 mg/kg via intra peritoneal route (i.p) to overnight fastening rats. On

3rd day 1ml blood was taken from tail for FBS from each rat. The rats whose blood glucose level was more than 250mg/dl were considered as diabetic.[18] Herbal extract and standard treatment were given to all the rats except positive control through metallic feeding syringe orally for a period of 28 days.

On 29th day, following overnight food deprivation, the rats were given an anesthesia that consisted of ether solution and were sacrificed as per Institutional Animal Ethics Committee (IAEC) guidelines. A blood sample of 10 ml was collected by cardiac puncture and was transferred into vacuum tubes which were then centrifuged at 3000 rpm for 10 minutes. After centrifugation, sera were separated for different biochemical assays.[19] Glycemic indices such as blood glucose level, serum insulin, Glycosylated Hemoglobin (HbA1c), serum amylase and lipid profile such as total cholesterol (TC), Triglycerides (TG), High density lipoprotein- Cholesterol (HDL-C), Very low density lipoproteins (VLDL- C), Low density lipoproteins - Cholesterol (LDL- C) were measured from serum samples by standard enzymatic methods using commercially available kits (Bartham, Trinder, Richmond and schettler) according to manufacturer advice respectively.

The data was analyzed using the software SPSS version 20.0. The glycemic índices and lipid levels were expressed as mean ± Standard Error of Mean (SEM) that were obtained by analysis of variance (ANOVA) test. The *P* values less than 0.05 were considered statistically significant for all treatment groups.

Results

Effects of Glycyrrhiza Glabra on Fasting Blood Glucose Levels

All the glycemic parameters showed a significant increase in the positive control group as compared to the negative control group at day 29 (Table I). A rampant decrease was observed in glimepiride group. The administration of licorice root extract at the dosage of 200mg/kg and 400mg/kg for 29 days to rats with hyperglycemia (induced by streptozotocin via intraperitoneal route of administration) a significant reduction in the blood glucose concentration, HbA1c and fasting serum insulin in comparison to the result obtained from the positive control group (mentioned in*).

Table I: Effect of Fasting Blood Sugar, Hba1c and Serum Concentration in Comparison With Negative and Positive Control

	FBG DAY 3	FBS DAY 29	HbA1C	Serum Insulin
Negative control	99.72 ± 3.44	103.94 ± 2.15	4.60 ± .44	3.34 ± .47
Positive control	492.16 ± 36.71*	613.33± 34.18*	14.78 ± 1.69*	7.76 ± .65*
Glimepiride	458.33 ± 7.36*	94.68 ± 3.05*	9.64 ± .294*	5.03 ± .16*
Metformin	494.16 ± 10.12*	116.63 ± 9.03*	9.29 ± .28*	5.38 ± .10*
GG 200 mg	447.00 ± 2.28*	285.70 ± 3.92*	14.78 ± 0.10	7.69 ± 0.18
GG 400 mg	451.16 ± 9.82*	259.79 ± 9.92*	14.69 ± 0.33	7.05 ± 0.15

GG: Glycyrrhiza Glabra
FBS: Fasting Blood Sugar
Glycosylated Hemoglobin
*shows P-value < 0.05 (highly significant)

Effects of Glycyrrhiza Glabra Root Onserum Lipid Concentration

Parameters associated with the lipid profile such as TC, TG, HDL- C, VLDL-C and LDL-C were considerably altered in positive control group in comparison with negative control (Table II). Rosuvastatin maximally normalized these values. Both doses of G. glabra also improved these parameters significantly as compared to positive control group (Table II).

Table II: Total Cholesterol TC, TG, HDL, VLDL, LDL, in Control and Diabetic Rats Treated With Glycyrrhiza Glabra

	TC	TG	HDL- C	VLDL	LDL
Negative Control	81.62 ± 1.78	39.43 ± 1.71	42.13 ± 1.59	7.79 ± 0.14	35.88 ± 1.17
Positive Control	264.88 ± 4.30*	211.78 ± 13.41*	32.79 ± 1.60*	54.54± 3.49*	124.45± .82*
Rosuvastatin	83.37 ± 1.80*	60.88 ± 0.96*	49.54 ± 0.50*	11.90± 0.51*	37.28± 0.60*
GG 200 mg	101.43 ± 2.76*	80.13 ± 1.07*	43.63 ± 1.41*	28.36 ± 1.40*	53.75± 0.77*
GG 400 mg	98.47 ± 1.26*	78.52 ± 1.47*	46.27 ± 0.65*	27.03 ± 1.63*	52.47± 1.33*

GG: Glycyrrhiza Glabra
TG: Triglycerides
TC: Total Cholesterol
HDL: High Density Lipoprotein
VLDL: Very Low-Density Lipoprotein
LDL: Low Density Lipoprotein
*shows p value is highly significant

Effects of Glycyrrhiza Glabra on Serum Amylase Levels

There was significant rise in serum amylase level in positive control group) when compared to negative control. G.glabra at both dosages reduced these values significantly (Table III).

Table III: Serum Amylase Level When Compared With Control Groups and G.Glabra Groups

GG: G.GLABRA

*shows p value is highly significant.

Groups	Serum Amylase(m.mol/L) ISD
Negative control	1142.83 ± 5.41
Positive control	1941.00 ± 139.41*
GG 200	1470.32±6.58*
GG 400	1487.21 ± 5.77*

Discussion

Management of diabetes by any means like with oral hypoglycemic drugs or by injecting drugs such as insulin or recently introduced exenatide[21] is a big challenge as nearly all of these drugs have a number of serious adverse effects and distressing complications. Moreover, these agents are generally used in combination to get maximum effects.[22] Finally, on enduring exploitation resistance develops gradually resulting in unsuccessful glucose control and appearance of fearsome complications.[22]

In this scenario the medicinal plants are great blessing as not only they have the potential to cure but also after diagnoses if received earlier herbal formulations derived from plants offer an innate approach for prevention of complications as well.[24] Hence for purpose of evaluating the anti-hyperglycemic properties of G.glabra we constructed a diabetic model of rats with streptozotocin.[25]

Firstly, it is to be noted that FBS values raised significantly at both doses of G. glabra i.e 200mg/kg and 400mg/kg as seen in table I and comparable with other studies done by Han S. *et al.*[26] The optimal blood glucose level must be below 140 mg/dl and this sugar level was achieved more or less only in standard groups. This finding can be attributed to the presence of non-hydrophilic flavonoids that showed alpha glucosidase inhibiting activity enzyme that hydrolyze polysaccharides into simpler form for better absorption of sugars from small intestine.[27] Other possible mechanism may be the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) as this receptor is responsible for the utilization of energy and homeostasis.[28] Our herb possesses both innate alpha-amylase inhibiting property along with natural PPAR-gamma inhibitory potential and thus modifies two different pathways of glucose metabolism which otherwise will be provided by two different classes of OHG agents.

Secondly, despite significant lowering of FBS after 29 days of treatment, G.glabra failed to improve HbA1c and fasting serum insulin levels when compared with positive control (p value 1.00). The underlying reason may be limited time duration of treatment i.e. 28 days which might be insufficient to produce obvious changes in HbA1c and insulin level.[1,9,29,30] As other studies conducted show that 12 month or greater time span yield in more positive result.[31] Thirdly, in our study the diabetic rats that were treated with G. glabra showed a considerable and significant improvement in all the parameters associated with dyslipidemia in comparison to the positive control group ($p<0.001$) just like the Rosuvastatin group. The anti dyslipidemic factor of G.glabra could be attributed to the presence of phytosterols and saponins in the G. glabra.[32,33,34,35] According to a study the phytosterol can replace the intestinal cholesterol which could lead to a decrease in the amount of cholestrol as it won't be absorbed properly from the intestine.[37] In one study, it was observed that when G. glabra roots when given as 5% and 10% diet for 4 weeks in hyper-cholesterolemic rats and it was observed that lipid levels were drastically reduced and excretion of cholesterol and bile acid seen in feces markedly increased.[35] In another study done by Shalaby *et al*. it was exhibited that G. glabra reduced the levels of TC and TG with no significant change observed in the levels of LDL, HDL and VLDL in male rats.[36] But these results are not consistent with our study as our results show a mark improvement in all parameters related to dyslipidemia which was also seen in Furukawa et al., 2017, Al-Rubeaan et al., 2017, King, 2012, Gaur et al., 2014.

According to the results of our study an increase in HDL and a decrease in TC is observed which can be owed to the increase stimulation of pre-β HDL-C and reverse cholesterol transport, as demonstrated in Rodriguez *et al's* study[38] or due to the suppression of hydroxyl methyl glutaryl-CoA synthase activity by Glycyrrhizin, the active component of G.glabra. The present study illustrated that research herb reduces the bad and improves the good cholesterol levels in streptozotocin induced diabetic rats which could be due to the saponin content of G.glabra root.

As pancreatitis is the common complication of few oral hypoglycemic drugs[39] and is usually encountered clinically as raised serum amylase levels.[17] Therefore,

we aimed to evaluate the effects of our herb on pancreatic enzymes and we found no aberration in this enzyme. The serum amylase levels were significantly increased in the diabetic rats in comparison to the rats in the positive control group. Furthermore the levels of serum amylase reduced back to an almost normal range after 28 days of treatment with G.glabra as seen in Table III.

This data is however scarce regarding the effects of this herb on pancreatic physiology but Xiaoying et al highlights the G.glabra's positive effect on the levels of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) in a cadmium induced hepatotoxicity of animal model and its reversal effect on inflammatory changes of liver.[40]

Conclusion

With the evidence from this study we conclude that G.glabra has significant glucose lowering effects with a striking protective role against dyslipidemia. As an alternative, this herb can be timely utilized for the management of diabetes and associated dyslipidemia without any obvious irregularity of pancreatic functions.

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