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Experimental Research

Biochemistry Section

Antihyperglycaemic and Antihyperlipidemic Effect of *Gymnema Sylvestre* in Protracted Diabetes Mellitus in Wistar Rats

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ABSTRACT

Introduction: Dysregulation in glucose and lipid metabolism have been observed in the early phases of Diabetes Mellitus (DM) which may further lead to insulin resistance and beta-cell failure. Effective control of these metabolic alterations may delay the clinical onset of diabetes. A proven herbal medication with antihyperglycaemic activity used in the treatment of Diabetes is *Gymnema sylvestre* (*GSE*). An extensive study regarding its benefits in treating long standing diabetes and associated dyslipidemia is obligatory.

Aim: To study the effects and optimal dosage of a standardized hydroalcoholic leaf extract of *GSE* on glycaemic and lipid parameters in diabetic rats.

Materials and Methods: Wistar rats of either sex were divided into five groups with eight rats in each group. Single dose of Streptozotocin (STZ) (50mg/Kg body weight) was used to induce DM. The diabetic rats were treated with two oral doses of the *GSE* at 1g and 2.5 g/kg body wt/day and Glibenclamide (Glb) (500 µg/kg body weight) for a period of 16 weeks. Fasting Blood Glucose (FBG) was checked at day-1 and at the end of 16 weeks. Plasma glycated Haemoglobin (HbA1c), serum insulin, serum Triacylglycerol (TG), Total Cholesterol (TC) and High Density Lipoprotein fraction of Cholesterol (HDL-C) were measured at the end of the study. Statistical analysis was done using the software SPSS-20.

Results: Significant decrease in FBG in a dose dependent manner was observed along with increase in serum insulin and decrease in HbA1c levels. Treatment with *GSE* decreased TG levels significantly and was comparable with Glb. Improvement in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was not significant, but that of Triglyceride Glucose Index (TGI) was significant. *GSE* at the dose of 2.5g/kg body weight showed a positive correlation between HOMA-IR and TGI (p=0.01) and was comparable with the results of Glb.

Conclusion: *GSE* had a sustained and dose dependent effect in improving glycaemic parameters and TG in diabetic rats of protracted duration. Insulin resistance did not vary significantly from the diabetic control rats.

Keywords: Diabetic rats, Insulin resistance, Lipid profile, Streptozotocin

INTRODUCTION

Glucotoxicity and lipotoxicity have been identified as the underlying pathologies in DM leading to insulin resistance and β-cell failure [1]. The dysregulation begins early in the process of development of diabetes and continues with a spiraling effect with the duration of the disorder. Both these with insulin resistance are known to contribute to the pathobiology of most of the diabetic complications exerting the effects through multiple mechanisms and severely compromising the quality of life in patients with diabetes [2].

Medicinal plants having hypoglycaemic and hypolipidemic activities have been tried in the treatment of diabetes with varying responses. A promising member of this family is *Gymnema sylvestre (GSE)* which has been well studied and the active principles characterized. *GSE* is a woody climber belonging to family: *Asclepiadaceae,* found in central and western India [3]. Anti-hyperglycaemic effect of a leaf extract of this plant has been described by Shanmugasundaram ER et al., and others [4-6]. Principal active chemical compounds responsible for this activity was known to be gymnemic acid which is a triterpenoid saponin in character [7]. The hypolipidemic activity as well of *GSE* plant was observed in non diabetic rats fed with high/normal fat diet [8]. The phytochemical, Dihydroxy gymnemic triacetate isolated from acetone extract of the leaves was noted to be responsible for hypolipidemic activity [9]. Administration of gymnemic acid was shown to increase fecal excretion of neutral steroids and bile acids in experimental animals [10]. *GSE* leaf extract has also been shown to have anti atherogenic [4,11] and *invitro* anti oxidant effects [12,13]. We have earlier reported that the levels of anti oxidants like vitamin C, glutathione and protein thiols in the tissue extracts of liver were found to be increased on long term treatment with extract of *GSE* on STZ induced diabetic rats [14]. Substantial evidence is not available as regards the long term efficacy of *GSE* in maintaining ambient glycaemic and lipid levels. Most of the previous studies which have shown an anti-hyperglycaemic and anti-hyperlipidemic activity of this plant were of shorter duration and thus the sustainability of these effects during prolonged usage remains uncertain.

Thus, the present study was aimed at evaluating the effects and optimal dosage of a standardized hydroalcoholic leaf extract of *GSE* on Fasting Blood Glucose (FBG), plasma glycated haemoglobin (HbA1c), serum insulin, serum lipid profile including Triacylglycerol (TG), Total Cholesterol (TC) and HDL-C in rats with STZ induced DM over a period of 16 weeks as against the reference standard hypoglycaemic drug, Glb.

MATERIALS AND METHODS

This was a cross-sectional experimental study conducted at Kasturba Medical College, Mangalore, Karnataka, India from January to December 2010.

Plant Extract

The required quantity (1kg) of *GSE* was procured from Natural Remedies Private Limited, Bangalore in a single batch. The

certificate of analysis claimed that this extract contains more than 25% w/w gymnemic acids. The powdered extract was dissolved in 0.5% carboxy methyl cellulose to prepare a solution and fed orally.

Animals Used

The experiment was conducted on Wistar albino rats of either sex, weighing 100±10gm. Rats were divided into five groups of eight rats each. An acclimatization period of one week was given before the experimental procedures were undertaken on the rats. Normal laboratory pellet diet and water were given to the rats *ad libitum*. The study was conducted after obtaining the ethical clearance from the Institutional Animal Ethics Committee of the institute, permission letter dated 20th Nov 2007 (213/PO/Re/S/2000/CPCSEA).

Induction of Experimental DM

Single dose of STZ (Sigma –Aldrich Corporation. 3050 Spruce St., St. Louis, Missouri 63103. United States) 50mg/Kg body weight, in cold citrate buffer (0.1M) of pH 4.0 was injected intraperitoneally, after 18-20 hours fasting for inducing DM [15]. These rats were monitored for 72 hours to ensure survivability. At day 1 of the experiment, FBG was checked with ACCU CHEK Active blood glucose monitor using disposable strips. Only those rats which showed FBG of 350mg/dl or more were selected for the study and distributed into different groups.

Experimental Procedure

Rats were divided into five groups, with eight rats in each group, as follows:

Group I, normal control;

Group II, STZ-induced diabetic control;

Group III, diabetic rats fed *GSE* (1g/kg body weight) daily via an intragastric tube for 16 weeks;

Group IV, diabetic rats fed *GSE* (2.5g/kg body weight) daily via an intragastric tube for 16 weeks and;

Group V, diabetic rats fed Glb (500 µg/kg body weight) in aqueous solution daily via an intragastric tube for 16 weeks [16].

At the end of 16 weeks, FBG was checked after an overnight fast and the rats were anaesthetized with high dose of ether. Blood was collected by cardiac puncture in EDTA tubes for HbA1c estimation and plain tube was used for estimation of insulin and lipid profile.

Analytical Methods

Determination of Insulin was done by ELISA (LINCO Research, 6 Research Park Dr.St.Charles, Missouri 63304 USA) technique following the manufacturer's instruction manual. HbA1c was estimated by Turbidimetric Inhibition Immunoassay (TINIA), TG by Glycerol – 3 - phosphate oxidase – peroxidase methods, TC and HDL-C by cholesterol oxidase-peroxidase method, on autoanalyser, HITACHI-917 using Roche kits.

HOMA IR was calculated by using the FBG and insulin values by the formula,

HOMA IR = {Fasting insulin (µunits/dl) x FBG (mg/dl)}/405 [17]:

TGI was calculated using the values of both FBG and TG by the formula;

TGI = log {fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/2} [18].

STATISTICAL ANALYSIS

Statistical software SPSS 20 (SPSS, Chicago, IL, USA) was used to analyse the grouped data. The results were expressed as the mean±SD for eight animals in each group. FBG was compared using paired sample t-test. One-way ANOVA with post hoc test was employed for comparison of mean between the groups. Pearson correlation test was employed to find the correlation of HOMA IR with TGI in different groups. The *p*-value of < 0.05 was taken as cut off for statistical significance.

RESULTS

[Table/Fig-1] shows the levels of FBG in control and test groups at day-1 and at the end of 16 weeks. There was a significant decrease in the levels of the same at the end of study in all the test groups ($p < 0.05$). The diabetic rats that received lower dose of *GSE* showed 30% decrease in FBG and the higher dose decreased it by 41%, whereas the standard drug Glb could decrease FBG by 28%. Both the normal control and diabetic control groups did not show significant variation from the initial levels till the end of the study.

[Table/Fig-2] shows the levels of serum insulin, HbA1c, TG, TC, HDL-C, HOMA-IR and TGI levels in different study groups at the end of 16 weeks. There was a significant decrease in serum insulin levels in diabetic control compared to normal control, and the levels of the same was improved in all treated groups compared to diabetic control. The levels of HbA1c were significantly increased in diabetic control compared to normal control and treatment with *GSE* lowered the levels. Glb also lowered the levels of HbA1c significantly compared to diabetic control. Increase in serum insulin and decrease in HbA1c among the two doses of *GSE* was dose dependent. TG levels were significantly high in diabetic control compared to normal control and were decreased significantly in all treated groups compared to diabetic control. The decrease in the levels of TC and improvement in HDL-C in rats which received the extract was not statistically significant compared to that of diabetic control. HOMA-IR was significantly higher in diabetic control compared to normal control group and improved upon treatment with *GSE* but the improvement in Glb treated group was better

	Group I	Group II	Group III	Group IV	Group V
Day-1	103.88±4.76	491.25±32.44	464.50±31.38	483.13±19.94	436.25±23.06
16th week	97.25±2.25	529.38±24.78	324.00±67.04*	285.63±74.55*	316.13±82.82*

[Table/Fig-1]: Comparison of FBG (mg/dl) between day-1 and 16th week in each experimental groups. (paired sample t-test).
(*- p≤0.05 compared to day-1)

	Group I	Group II	Group III	Group IV	Group V
Insulin(ng/ml)	0.64±0.13	0.14±0.03*	0.41±0.03†	0.56±0.05†,‡	0.27±0.14*,†
HbA1c(%)	3.66±0.17	7.68±0.73*	7.09±0.64	6.43±0.36†	6.74±0.62†
TG (mg/dl)	74.13±11.62	111.00±6.28*	60.13±5.22†	58.75±3.92 †	82.25±13.30†
TC (mg/dl)	60.75±6.82	62.50±10.13	66.0±6.85	63.12±6.36	67.50±11.45
HDL-C (mg/dl)	55.13±7.55	51.13±10.86	51.38±7.93	51.63±6.76	56.38±7.56
HOMA IR	0.0129±.00	0.0550±.02*	0.0270±.01*	0.0328±.01*	0.0176±.01*,†
TGI	9.83±0.40	14.76±0.23*	11.79±0.56*,†	11.43±0.77*,†	12.56±0.74*,†

[Table/Fig-2]: Comparison of 16th week plasma HbA1c, serum insulin, TG, TC, HDL-C, HOMA IR, TGI between all the experimental groups (oneway ANOVA with post hoc test).
(*- p≤0.05 compared to normal control, † p≤0.05 compared to diabetic control, ‡ p≤0.05 compared to diabetic+Glb).

compared to *GSE* treated groups. TGI also was more in diabetic control compared to normal control. Treatment with GSE improved the value, similar observation was found even with Glb treatment. *GSE* at higher dose of 2.5g/kg body weight could bring the TGI down significantly compared to Glb treated group.

[Table/Fig-3] explains the correlation between HOMA-IR and TGI among the different study groups. No correlation was observed in control groups. A statistically significant correlation between the two estimated parameters was seen in all the three treated groups. *GSE* at the dose of 2.5g/kg body weight showed significant correlation (p=0.01) and this was comparable with that in the group treated with Glb.

Group name	Correlation of TGI with HOMA-IR (r-value)
Group I	-0.226
Group II	-0.286
Group III	0.719*
Group IV	0.975**
Group V	0.960**

[Table/Fig-3]: Correlation between HOMA-IR and TGI among individual experimental groups.
**. Correlation is significant at p < 0.01 level, *. Correlation is significant at p < 0.05 level, as per Pearson's correlation.

DISCUSSION

This study was designed to study the outcome of *GSE* on glycaemic and lipid profiles in animal model of protracted diabetes, *GSE* treatment for a period of 16 weeks resulted in a statistically significant improvement in the glycaemic parameters, the higher dose being equivalent to Glb, indicating its effectiveness in reducing hyperglycaemia even at the end of 16 weeks of treatment. One of the previous studies showed that an extract of *GSE* for eight weeks brought back glucose homeostasis, which was appreciated by increased serum insulin levels [5]. The effect of an alcoholic extract of *GSE* on insulin secretion from islets of Langerhans and several pancreatic β-cell lines were examined by Persaud SJ et al., [19]. STZ is a drug that is selectively toxic for insulin producing/secreting cells. In moderate doses, (45mg/kg) it causes insulin resistance by a decreased autophosphorylation of insulin receptors [20]. Such a moderate dose of STZ was selected in the present study so that it might have produced a partial destruction of β-cells. However, in the present study, the increase in insulin levels in the rats treated with the higher dose of *GSE* was significantly higher compared to Glb indicating that *GSE* may have a better insulinogenic activity as compared to Glb.

HOMA-IR showed a better result in Glb treated group compared to *GSE* treatment. Glb along with being insulin secretogogue, may also increase the sensitivity of existing insulin receptors and optimal utilization of the same [21]. *GSE*, fed for one week, could not improve insulin resistance in STZ- diabetic rats [22]. This may be the possible reason for the present observation of higher HOMA-IR in spite of improved insulin levels in *GSE* treated groups compared to Glb.

GSE decreased the levels of TG significantly and the values were brought to near normal in all test groups. Thus, anti hyper triglyceridemic activity of this extract is well established in this study. This effect of *GSE* is significantly higher compared to treatment with Glb. Glb is not well appreciated by the earlier workers as a drug to regulate lipid profile [23]. In contrast, the present study depicted a significant decrease in TG on treatment for 16 weeks. This significant reduction may be due to a longer study period as compared to the previous studies. There was no significant increase in serum TC of diabetic control rats. This might be the reason for not observing a significant decrease of TC in *GSE* treated as well as Glb treated rats on comparison with diabetic control. Thus hypocholesterolemic effect could not be observed. This finding of ours is in agreement with that of Wang X et al., [24]. The most characteristic lipid abnormality in diabetics is hyper triglyceridaemia, with or without associated increase in plasma cholesterol [10]. Development of both micro and macrovascular changes of diabetes may be ameliorated by controlling hyperlipidemia [25]. Shigematsu N et al., showed that the serum lipids were normalized by the leaf extract of *GSE*, when fed orally for 10 weeks to the rats receiving a high fat diet and decrease in TG was observed in the rats receiving a normal fat diet [26]. In a clinical trial by Preuss HG et al., *GSE* extract at a dose of 400mg/day along with hydroxyl citric acid and niacin bound chromium given to moderately obese individuals for eight weeks decreased TC, LDL-C and TG contents significantly, with increased serum HDL-C [27]. The rich content of gymnemic acids, saponins and the increased fecal excretion of neutral steroids and bile acids by the administration of *GSE* leaves may be responsible for the findings [28]. TGI, a product of FBG and TG, is a marker of insulin resistance and type-2 DM [29,30]. Guerrero-Romero F et al., introduced this calculated parameter of TGI as a surrogate marker of insulin resistance [31]. Evidences stipulate that hepatic lipid species like TG, diacylglycerol, fatty acyl CoA and ceramides contribute to insulin resistance by selectively interfering with insulin-signaling [32]. In the present study, a significant decrease in TGI in treated groups may be an indicator of improvement of insulin resistance. Further, HOMA-IR showed a good correlation with TGI in all the treated groups, higher dose of *GSE* showing excellent correlation comparable with Glb. Thus, we suggest TGI as an emerging marker of insulin resistance along with HOMA-IR.

The present study thus provides evidence for the protective effect of *GSE* over a longer period in controlling both hyperglycaemia and associated hypertriglyceridemia.

LIMITATION

Insulin receptor study could not be performed to know exactly whether *GSE* shows any improvement in the number of receptors. A study in this regard may be envisaged in future. Further multiple dosages may be used for a better selection of optimum dosage of *GSE*. Further controlled studies are needed to explore the mechanisms involved in bringing about the said benefits and safety of this plant extract in controlling DM.

CONCLUSION

GSE showed sustained anti hyperglycaemic and anti hypertriglyceridemic effects in a dose dependent manner plausibly through insulinogenic properties as indicated by increased serum insulin levels. However, insulin resistance was not improved up on treatment with *GSE*.

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