ORIGINAL ARTICLE

Hypoglycemic activity of *Qurse Tabasheer*, a Unani formulation, in chemically induced diabetic rats

Md Nazamuddin, Abdul Wadud, Najeeb Jahan

Department of Ilmul Advia (Pharmacology), National Institute of Unani Medicine, Bengaluru, Karnataka, India

Abstract

Background: Diabetes mellitus (DM) is the third leading cause of death; its prevalence is about 6% worldwide. Conventional management of DM is satisfactory but often associated with adverse effects. Unani Medicine offers effective anti-hyperglycemic drugs. The aim of the present study was to evaluate the hypoglycemic activity of *Qurse Tabasheer* (QT) in streptozotocin (STZ)-induced rat model. **Materials and Methods:** Adult Wistar rats of either sex were divided into five groups of eight animals each. The animals of plain control were given distilled water throughout the study. Diabetes was induced by single dose injection of STZ (IP, 50 mg/kg) in 0.1M Citrate buffer, in all the animals of each group except plain control. From the 10th day, Test groups A and B were treated with QT (583 and 1166 mg/kg), respectively, while standard group was treated with Glibenclamide (600 µg/kg). The treatments were continued for 56 days. Blood samples were taken on 0th, 10th, 28th, and 56th days. The effect of test drug was assessed by measuring body weight, fasting and postprandial blood glucose, hepatic glycogen content, lipid profile, and glycosylated hemoglobin. The data were analyzed statistically using repeated measures analysis of variance tests with Tukey–Kramer Multiple comparison test. **Results:** Body weight of animals of the test and standard groups significantly increased ($P < 0.001$) on 56th days; fasting blood glucose level decreased in Test groups A and B. Postprandial glucose level significantly decreased in standard group ($P < 0.05$). HbA1C decreased significantly ($P < 0.01$) in the Test groups A, B, and standard groups. Hepatic glycogen and lipid profile also normalized in the Test groups A, B, and standard groups. **Conclusion:** On the basis of above results, it can be concluded with certain limits that the test drug possesses hypoglycemic potential.

Key words: Diabetes mellitus, hypoglycemia, *qurse tabasheer*, streptozotocin, unani medicine

INTRODUCTION

Diabetes mellitus (DM) is the most common non-communicable disease. Its incidence is rising at an alarming rate.[1] It is estimated that 20% of global burden of DM resides in South East Asia Region, which is likely to triple by 2025.[2] This disease can be managed by the use of anti-hyperglycemic drugs, but the management without any adverse effects is a task for medical science. Search for safe anti-hyperglycemic agents from plant source has become a thrust area of research nowadays. As an alternative approach, herbal drugs with hypoglycemic activity are increasingly sought by many diabetic patients.

DM can be induced experimentally in animals[3] by damaging the pancreas by certain chemicals. Streptozotocin (STZ)-induced DM in animals is used by most researchers. It induces diabetes in rabbits[4] rats,[5] mouse,[6] golden Syrian hamster, and Yorkshire Landrace Pigs etc.[7] Being a good model for assessing the efficacy of hypoglycemic drugs, this model is frequently used by the researchers.

Qurse Tabasheer (QT) is a Unani formulation consisting of *Tukhme Khurfa* (*Portula olaracea* L.), *Tabasheer* (*Bambusa arundinacea* [Retz].Willd.), *Gulnar* (*Punica granatum* L.), GuleSurkh (*Rosa damascene* Mill.), *Tukhme Kahu* (*Lactuca scariola* L.), and *Gile Armani* (Armenian bole), which is claimed to be effective in the management of DM.[8] Some ingredients of QT have sufficient evidence of the efficacy and

Address for correspondence:
Abdul Wadud, Department of Ilmul Advia (Pharmacology), National Institute of Unani Medicine, Bengaluru, Karnataka, India. Mobile: 91-9916608881.
E-mail: drwadud87@gmail.com

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have also been evaluated scientifically. Oral administration of *P. oleracea* reduced the blood sugar level in alloxan-induced diabetic rabbits to normal.[9] The hypoglycemic activity of entire plant was shown in rabbits at a dose of 1.5 and 2 g/kg after 8 and 12 h.[10] Oral administration of hydroalcoholic extract of *P. granatum* flower lowered blood glucose significantly in normal glucose-fed hyperglycemic and alloxan-induced diabetic rats.[11] The oral administration of *P. granatum* peel extract in normal and STZ-induced diabetic rats showed a significant decrease in the post prandial hyperglycemia.[12] No scientific data are available to confirm hypoglycemic activity of QT. Therefore, it was evaluated on scientific parameters for its claimed efficacy in STZ-induced DM in rat.

MATERIALS AND METHODS

Preparation of drugs

The ingredients of QT enlisted were procured from the local market of Bangalore, dried well in shade, cleaned, and powdered in an electrical grinder; used in powder form.

Preparation and dose of drugs and of reagents

The human therapeutic dose of QT mentioned in Unani literature is 5 g.[8] The dose for Wistar rat was calculated by the conversion factor "7"[10] and was found as 583 mg/kg. To evaluate the dose-dependent effect, this dose was doubled. Citrate buffer was prepared by mixing 50% 0.1M Citric acid solution and 50% 0.1M Tri Sodium Citrate. STZ 100 mg vial was suspended with 5 ml of 0.1M Citrate buffer and was administered immediately.

Animals

Healthy Wistar rats of either sex; weighing 150–200 g; 2–3-month-old obtained from Biogen Laboratory Animal Facility, Bangalore, were acclimatized to the laboratory condition for 7 days. The animals were housed in polypropylene cages and kept under the standard environmental condition of 12 h light and dark cycle, humidity (55 ± 15%), had access to standard food pellets and water *ad libitum*. The study was carried out after approval of the protocol by the Institutional Animal Ethics Committee (IAEC) of National Institute of Unani Medicine, Bangalore vide no. IAEC/VIII/03/IA.

Experimental Design for the evaluation of QT on STZ-induced DM.

The study was carried out by the method of Rakieten *et al*., and Van Zwieten (1963)[11,13] with some modification in the treatment schedule. Forty rats were divided into five groups of eight animals each as plain control, received single-dose Citrate buffer 0.1M, i.p. and left untreated for 10 days followed by distilled water 1 ml/kg; orally, negative control received Inj. STZ, 50 mg/kg, i.p. and left untreated for 66 days; Test group A received Inj. STZ, 50 mg/kg, i.p. + QT (583 mg/kg) dissolved in 5% gum acacia, suspended in 1 ml distilled water, orally and Test group B received Inj. STZ 50 mg/kg i.p. + QT (1166 mg/kg) dissolved in 5% gum acacia, suspended in 1 ml distilled water, orally, and standard group, received Inj. STZ 50 mg/kg, i.p. + Glibenclamide (600 µg/kg).

Assessment of hypoglycemic activity

Blood samples were taken through heart puncture for estimation of glycogen content and lipid profile at the end of the study. At the end of the 66th days, animals were sacrificed under Thiopentone sodium anesthesia (40 mg/kg i.p.)[13] Liver tissue was taken for estimation of hepatic glycogen. The effect of the drugs was assessed by measuring body weight, fasting blood glucose (FBG), postprandial blood glucose (PPG), hepatic glycogen, glycosylated hemoglobin (HbA1C), and lipid profile. Plasma glucose levels were estimated using commercially available glucometer based on oxidase method SD Code Free, Standard Diagnostic, Korea. The fasting and postprandial plasma glucose levels were estimated on 0, 10th, 28th, and 56th days of experiment by pricking the tip of tail. The absorbance of each standard glucose solution was measured against the blank using a spectrophotometer at a wavelength of 630 nm. Blank was prepared in the same way by replacing glucose solution with 1 ml of distilled water.[14] HbA1C was estimated by autoanalyzer with the help of commercially available kit based on total glycohemoglobin ion exchange resin method, Euro Diagnostic System Pvt. Ltd., Chennai. Cholesterol was estimated by autoanalyzer with the help of commercially available kit based on CHOD-POD Method, Rapid Diagnostic Pvt. Ltd., Delhi. Triglyceride was estimated by autoanalyzer with the help of commercially available kit based on GPO-POD Method, Rapid Diagnostic Pvt. Ltd., Delhi. High-density lipoprotein (HDL) cholesterol was estimated by autoanalyzer with the help of commercially available kit based on CHOD-POD Method, Rapid Diagnostic Pvt. Ltd, Delhi. The values of low-density lipoprotein (LDL) were calculated by Friedewald formula, LDL = Total cholesterol – HDL – very-LDL (VLDL); VLDL = Triglyceride/5.

Statistical analysis

The data were tabulated and the statistical analysis was performed by analysis of variance (ANOVA) repeated and Tukey–Kramer Multiple comparison test. The significance level was set at $P < 0.05$.

RESULTS

Effect on body weight

STZ administered to all the groups except Group I (plain control), brought about marked reduction in body weights of

rats. The normal increase in the body weight was observed in plain control throughout the experiment, that is, from 0 day to 66th days. The reduced body weight in treated groups was found to be increased when compared with negative control (group II), after treatment with test drug and standard drug from 10th days onward. At 28th days, the increase in body weight in rats of Groups III, IV, and V was found to be significant ($P < 0.01$), when compared with negative control. At 56th days, the increase in body weight in rats of Groups III, IV, and V was found to be significant ($P < 0.01$), when compared with Group II and was toward Group I. Increase in body weight was found to be 8.28% in Group III, 33.74% in Group IV, and 14.61% in Group V after 56 days of treatment. As far as the relative increase or maintaining body weight is concerned, double dose of test drug seems to be the most promising than single dose of test drug and standard drug, as the increase in body weight was found to be significant ($P < 0.01$) in high-dose-treated group of test drug than the standard drug and low dose of test drug-treated group [Table 1].

Effect on FBS

The mean values of the plasma glucose on 0, 10th, 28th, and 56th days of experiment were compared. Mean and mean differences of plasma glucose level were calculated. STZ causes selective destruction of β-cells of islets of pancreas and brings an increase in blood glucose levels. It is evident from the present investigation that STZ administration at the dose of 50 mg/kg body weight to the animals of negative control, test Groups A and B as well as standard group, caused significant diabetogenic response as FBS was found to be increased in all the animals of each group from 0th day of STZ administration increased levels stabilized till 10th days. After 28 days of treatment, the fasting blood sugar levels were found to be decreased in test Groups A, B, and standard group. When comparisons were made between negative control and test drug-treated group animals, blood glucose levels declined sharply from 28th days to 56th days. After 56 days of treatment, the decrease in fasting glucose levels was found to be strongly significant ($P < 0.01$) in Test groups A, B, and standard group [Table 2].

Effect on postprandial glucose

On 0 day, just after induction of DM and on 10th days PPG levels raised significantly ($P < 0.001$) in STZ-treated groups when compared with plain control. After 28th days, it was found to be moderately decreased in test group Band standard group ($P < 0.05$) when compared with negative control. After 56th days, PPG level decreased moderately ($P < 0.05$) in test Group B, while, in the standard group, greater reduction was observed ($P < 0.01$) when compared with group negative control [Table 3].

Effect on glycogen content

From the standard glucose calibration curve, it was found that optical density/or absorbance of the test sample (glycogen from the liver extract of rats of five groups) when corresponded to the concentrations of 0 µg, 20 µg, 40 µg, 60 µg, 80 µg, and 100 µg/ml standard glucose, the quantity of liver glycogen decreased significantly ($P < 0.05$) in STZ-treated groups in comparison to plain control. After treatment with test and standard drugs, it increased in respective groups but not found statistically significant ($P > 0.05$) [Table 4].

Effect on HbA1C

The values of HbA1C significantly increased ($P < 0.01$) in STZ-treated group with respect to negative control. Value of HbA1C decreased significantly ($P < 0.01$) in Test groups A, B, and standard group when compared with negative control [Table 4].

Effect on lipid profile

The values of TC, TGL, LDL and VLDL in the blood increased significantly ($P < 0.01$) in the rats of STZ treated groups II (Negative control) with respect to Group I (Plain control). But value of TC, TGL, LDL and VLDL decreased significantly ($P < 0.01$) of animals treated with test drug and standard drug, returned to values nearing that of the Plain control group. The value of HDL was significantly decreased ($P < 0.01$) in Group II (Negative control) when compare with Group I (Plain control) but test group and standard group showed significant increase ($P < 0.01$) when compared to negative control [Table 5].

DISCUSSION

The goal of the management of type 2 diabetes is to control fasting plasma glucose and HbA1c levels. This goal is achieved by most conventional anti-hyperglycemic drugs. In recent years, herbal remedies for chronic medical problems are gaining status. QT is claimed to be effective in diabetes.[14,15] Some of its ingredients such as *P. granatum* and *P. oleracea* have been scientifically evaluated for hypoglycemic effete.[16,17] In the present study, QT has been investigated for its hypoglycemic activity in STZ-induced diabetic rat model.

STZ is an antibiotic derived from *Streptomyces achromogenes* and structurally a glucosamine derivative of nitrosourea. It causes hyperglycemia mainly by its direct cytotoxic action on the pancreatic beta-cells.[18,19] The present study was designed by including a number of tests and parameters that commensurate with different pathophysiological aspects and mechanism associated with DM so that the test drug can be studied comprehensively for hypoglycemic effect. The parameters like body weight and the tests included were

Table 1: Effect of test drug on body weight in STZ-induced diabetes mellitus

Groups	Weight (g)			
	0 day	10th day	28th day	56th day
Group I (Plain Control)	195.62±2.04	202.75±2.48	208.87±1.28	211.37±0.92
Group II (Negative Control)	224.5±1.64	190.12±2.78	182.87±1.24	180±1.03
Group III (Test Group A)	181.87±1.52	138.12±1.34	141.12±1.26[a**]	196.12±0.97[a**]
Group IV (Test Group B)	163.25±1.19	148.87±1.43	150.12±1.34[a**b*]	218.87±1.48[a**b**c**]
Group V (Standard Control)	171.87±1.12	156.87±0.97	172.17±1.49[a**b*c*d**]	196±1.11

n=8, Values-Mean±SEM. Test used: ANOVA tests with Tukey–Kramer Multiple comparision test. [a]Test group A, Test group B, standard group versus negative control, [b]Test group A versus test group B, [c]Test group A versus Standard group, [d]Test group B versus standard group *P<0.05, **P<0.01

Table 2: Effect of test drug on fasting blood glucose in STZ-induced diabetes mellitus

Groups	FBS (mg/dl)			
	0 day	10th day	28th day	56th day
Group I (Plain Control)	74.87±2.33	71.75±1.93	74±1.80	86±2.04
Group II (Negative control)	71.25±2.11	190.5±25.64[a*]	232±19.06	326.5±11.62
Group III (Test group A)	80.12±1.92	70.37±19.48	296.87±8.04[c**]	188.5±17.87[b**]
Group IV (Test group B)	75.87±2.04	162.25±22.81	204±12.87	135.37±8.5[b**]
Group V (Standard control)	70.62±2.29	183.87±3.81	97.87±13.92	190.87±7.80[b**]

n=8, Values-Mean±SEM, Test used: ANOVA tests with Tukey-Kramer Multiple comparison test [a]Negative versus plain control, [b]Test group A, test group B, Standard group versus negative control, [c]Test group A versus test group B **P<0.01

Table 3: Effect of test drug in postprandial glucose in streptozotocin-induced diabetes mellitus

Groups	Blood sugar (mg/dl)			
	0 day	10th day	28th day	56th day
Group I (Plain control)	84.87±3.89	97.62±2.33	118.25±3.09	119.12±4.16
Group II (Negative control)	246.25±17.98	396.12±22.03	472.37±18.41	450.37±4.33
Group III (Test Group A)	171.37±10.53	503.75±13.77	424.37±40.70	390.37±5.44
Group IV (Test Group B)	230.5±12.05	495.12±22.25	384.87±30.26[a*]	360.12±3.91[a*]
Group V (Standard control)	223.25±10.37	500.75±4.90	339.37±28.28[a*]	354.12±3.96[a**]

n=8, Values-Mean±SEM., Test used: ANOVA tests with Tukey-Kramer Multiple comparision test [a]-Test group B, standard group versus negative control*P<0.05, **P<0.01

Table 4: Effect of test drug on glycogen content

Groups	Glycogen Content	HbA1C %
Plain control	28.87±1.77	7.36+0.32
Negative Control	14.25±0.95[a*]	14.6±0.67[a**]

n=8, Values: Mean±SEM, Test used: ANOVA tests with Tukey–Kramer Multiple comparison test [a]Negative control versus plain control, [b]Test group A, test group B, standard group versus negative control *P<0.05,** P<0.01

FBG, PPG level, HbA1C, lipid profile, and glycogen content in liver tissue for assessing the efficacy of hypoglycemic drugs in DM.

A person with untreated DM suffers metabolic abnormalities that can cause severe wasting of the body tissues.[20] After STZ administration marked reduction in body weight was observed in all groups, except plain control. It increased after treating with test and standard drugs, from 10th days of STZ administration onward. At 28th and 56th days, body weight of the animals of test and standard groups increased significantly (P < 0.01) when compared with the animals of plain control demonstrated the hypoglycemic effect of the test drug. A marked increase in weight (33.74%) in Test group B indicated a dose-dependent effect.

Inhibition of gluconeogenesis and reduction of absorption of glucose are important pharmacological approach. After STZ administration, FBG levels increased in test and standard groups on 10th days when compared with plain control. On 56th days after administration of test and standard drug in respective groups, the mean FBG levels decreased when compared with negative control. No significant difference

Table 5: Effect of test drug on lipid profile

Group	Lipid profile (mg/dl)				
	T. Cholesterol	HDL	TGL	VLDL	LDL
Group I (Plain Control)	94±2.75	48.5±4.69	62.75±4.84	12.55±0.96	33.57±5.46
Group II (Negative control)	241.62±18.49	23.75±1.61	35.12±6.22	7.02±1.24	205.35±9.46
Group III (Test group A) Group	146.25±4.22^{a**}	61.75±4.58^{a**}	103.12±11.53^{a**}	20.62±2.30^{a**}	63.87±7.21^{a**}
Group IV (Test group B)	146.62±4.15^{a**}	42.75±3.06^{a**}	78.5±4.65^{a**}	15.7±0.93^{a**}	88.17±4.76^{a**}
Group V (Standard control)	184±13.14^{a**}	53.37±4.11^{a**}	96±9.38^{a**}	19.2±1.87^{a**}	127.8±14.01^{a**}

n=8, Values-Mean±SEM, Test used: ANOVA tests with Tukey–Kramer Multiple comparison test [a]Test group A, test group B, and standard group versus negative control **P<0.01

was observed in test and standard groups. Therefore, the effect was thought to be insulin like.[21]

Control of PPG in diabetes is a good aspect.[22] Reduced PPG between 22.54% and 27.23% in single and double dose of the test drug indicated that test drug acted in a dose-dependent manner. The possible mechanism in this regard maybe either increased secretion of insulin or reduction in absorption of glucose from the intestine as shown by previous studies. The latter may be due to *Gile Armani* as it coats the intestine.

The liver plays a crucial role in maintaining blood glucose. The reduced glycogen content was observed in diabetic rats. The findings showed increased glycogen quantity ($P > 0.05$) in Test group A. In the present study, the HbA1C increased significantly ($P < 0.01$) in negative control but decreased significantly ($P < 0.01$) in test and standard groups. It could be due to improvement in insulin secretion. A marked feature of DM is dyslipidemia, especially increased triglycerides and total cholesterol. In this study, the test drug decreased triglycerides, total cholesterol, LDL and VLDL, and increased HDL cholesterol. The results clearly demonstrated the efficacy of QT as it significantly reduced the biochemical parameters in STZ-induced type 2 DM. The effect of the test drug was found to be more pronounced in higher dose; further, it was found to be comparable to standard drug Glibenclamide.

Earlier investigations of chemical constituents and their pharmacology revealed that flavonoids and glycosides possess hypoglycemic activity. The phytochemicals have also been reported to be present in some of the ingredients of QT, having hypoglycemic effect. In a study, oral administration of *P. oleraceae* reduced the blood sugar level in chemically induced diabetic animals.[16] *R. damascena* contains a bitter principal, tanning matter consisting of cyanine, a yellow glycoside of quercetin, and a yellow crystalline dyestuff. Rosebuds are astringent moreover, tannin occurs in all part of the *P. granatum*. Oral administration of its flower extract lowered glucose in normal, glucose-fed hyperglycemic, and alloxan-induced diabetes.[17] In addition, the oral administration of *P. granatum* peel extract in normal and STZ-induced diabetic rats showed a significant decrease in the post prandial hyperglycemias.[23] *Tabasheer* consisting of 70% of silica and 30% of potash and lime,[24] Silicate of alumina or magnesia and oxide of Armenian bole may have acted as a barrier for glucose absorption.[25,26] Hence, the hypoglycemic effect of test drug may be attributed to the presence of these phytochemicals.

Anti-hyperglycemic drugs act mostly by insulin-like properties.[27] In this study, the effects cannot be claimed due to increased insulin secretion as no such activity is reported in any of the ingredients of QT. Most herbal hypoglycemic drugs are said to exert their action by decreasing the absorption of glucose by intestine.[28] Astringent and glutinous properties of some of the ingredients may have decreased glucose absorption; however, insulin-mimetic activity cannot be ruled out at all.

CONCLUSION

On the basis of results and discussion, it is concluded that the test drug has significant anti-hyperglycemic effect. Since the test drug produced dose-dependent effect without any observable side effect; therefore, it can be used in higher dose but after toxicity studies. The study validated the use of QT in the treatment of diabetes in Unani medicine; however, further studies are required to utilize this drug as evidence-based drug.

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