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Antidiabetic effect of grape seed (OPC 95%) powder on nSTZ-induced type 2 diabetic model rats

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Grape seeds (GSs) have been claimed for antidiabetic effects since long. Due to its rich phytochemical potential, current study was aimed to evaluate the antidiabetic effect of GSs powder (GSP) (OPC 95%) on neonatal streptozotocin (nSTZ) induced T2DM rats. STZ (90 mg/kg) was administered intraperitoneally in 48 h old rat pups. After 3 months, 24 T2DM rats were selected by OGTT for 28-days experiment and divided into four groups (n=6): group I: Normal water control [NWC], group II: Diabetic water control [DWC] (10 mL ddH_2O/kg bw), group III: Gliclazide treated [GT] (20 mg/kg bw) and group IV: GSP treated group (1.25 g/kg/ bw). Blood were collected by tail cut and cardiac puncture method during the begging and end of the experiment respectively and thereafter serum was separated. Liver was also collected and all samples stored at -20°C freezer until the measurement of fasting serum glucose (FSG), lipid profile, insulin level and liver glycogen content by following standard methods. Statistical analysis was performed considering one-way ANOVA and paired t-test. Oral consumption of GSP significantly (P<0.009) reduced FSG and increased serum insulin (p<0.001) compared with base line value. GT group also ameliorated FSG significantly (p<0.001) compared to DWC group. Moreover, liver glycogen content was also improved by 16% compared with DWC group. Additionally, TG, TC and LDL were significantly reduced (p<0.002, p<0.01, p<0.05 respectively), HDL was increased by 4% through consecutive GSP treatment. Current results suggest that GSP possesses a significant hypoglycemic effect in T2DM rats.

Key words: Grape seed powder, T2DM, streptozotocin, glycemic status.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder which is characterized by insufficient insulin production from pancreatic beta cell or when the body cannot make proper use of their insulin (Mellitus, 2005). Chronic hypoglycemia associated with defects in an imbalance between insulin secretion or insulin action and long-term

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chronic hypoglycemia responsible for damaging, dysfunction, and failure of various organs, chronic heart disease, and malnutrition renal failure, liver diseases such as hepatitis and cirrhosis as well as kidney disease (WHO, 1999; Shafiee et al., 2012). According to the International Diabetic Federation (IDF), worldwide 463 million of the people are suffering from diabetes and in 2045, the number of diabetic cases will be raised to 700 million due to their uncontrolled diet, life style, and malnutrition related problem. In Bangladesh 8.4 million people are affected by diabetes and subjects are prediabetes (that is, IFG & IGT) will be raising 15 million in 2045 (Borgnakke, 2019). Therefore, this estimation has become a serious health concern for the practitioners and pharmaceutical management globally. Moreover, without any side effects, the therapeutic management of diabetes is still challenging in medical science. So, for diabetes management, alternative medicine is required to control this disorder. Plants are important natural materials that are used for treatment of many diseases (Sevindik et al., 2017; Mohammed et al., 2020, 2021). Islam is a religion of the ideal complete code of life. The name of the grape appears as “Inab” and it is narrated eleven times in the Holy Quran (Urbi et al., 2014). *Vitis vinifera* L. (Grape) seeds containing major phytochemicals are flavonoids, organic acid, tannins, proanthocyanidins, procyanidins, catechin, epicatechin, gallate, vitamins and minerals where catechin inhibits intestinal glucose absorption, epicatechin restoring pancreatic β-cell regeneration, epicatechin gallate expands hepatic glycogen synthesis and the antioxidant effects by phenolic compounds such as oligomeric proanthocyanidins (OPCs) (Weber et al., 2007; Pinent et al., 2004; Kanagarla et al., 2013). Moreover, procyanidins and anthocyanidins promote the GLUT 4 translocation by activating AMPK pathways and exert their integral role in the management of diabetic complication (Pinent et al., 2004; Mohankumar et al., 2013). Grape (red) seed also inhibits the α-glucosidase, protein glycation products (PG) and exhibit antihyperglycemic effect (Jariyapamornkoon et al., 2013; Salim, 2018; Yildirim et al., 2020). Additionally, in the STZ induced diabetic rat model, grape seeds powder solution decreased the levels of lipid peroxides and carbonylated proteins and enhanced the antioxidant activity (Hogan et al., 2010). In this perspective, the present study was designed to explore the plausible antidiabetic action regarding changes of some biochemical parameters (glucose, insulin and liver glycogen) in nSTZ induced type 2 diabetic model rats by treating grape seeds powder (OPC 95%).

MATERIALS AND METHODS

Plant and phytochemistry

Grapes seeds powder was collected from commercial market of Dhaka City, Bangladesh. The fine powder was directly used for preliminary phytochemical screening. 3 g grape seed powder was dissolved with 30 mL distilled water and kept in water bath at 85 to 90°C for 5 min. The hot sample solutions were filtered by using filter paper (Whatmann No. 1). Then the filtrate was taken for testing the presence of phytochemicals following the standard protocol (Gayathri and Kiruba, 2014; Harborne, 1998).

Test for alkaloids

Hager’s test: 1 mL of the sample was treated with 2 mL of Hager’s reagent and a formation of yellow precipitate indicated the absence of alkaloid in sample solution.

Tannins test

One milliliter of cool filtrate sample was mixed with 5 mL of distilled water and few (2-3) drops of 10% Ferric chloride were added and observed for any formation of bluish black/brown green color, which indicated the presence of tannins.

Phenols test

Two milliliters of cool filtrate sample solution were treated individually with 1 ml of potassium-ferro-cyanide and freshly prepared 1% ferric chloride solution, presence of bluish green color that indicated the presence of phenols in the sample solution.

Terpenoids and steroids test

1mL of cool filtrate sample as mixed with chloroform and few drops of concentration H2SO4 then shaken carefully and allowed to stand for few times. The red color was absent in the upper layer indicated steroids was absence and the yellow color in lower layer indicated terpenoids.

Saponins test

Froth test: 2.5 mL of cool filtrate sample was diluted to 10 mL of distilled water and shaken vigorously for 3 min and formatted of frothing indicating the presence of saponins

Flavonoids test

(i) Mg ribbon test: 1 mL of the sample was added along with diluted HCl from sides of test tubes. Few fragments of magnesium ribbons were also added to the test tubes. Presence of slight pink color in the test tubes indicated the presence of flavonoids in the sample.
ii) Few drops of NaOH solution were added to 5 mL of the sample. Formation of an intense yellow color, which turns to colorless on addition of few drops of diluted H_2SO_4 indicated the presence of flavonoids in sample.

Animals

Twenty four adult Long Evans rats weighing 168 to 190 g were selected for the current study. The animals were bred at Bangladesh University of Heath Sciences animal house. The animals were housed in plastic cages and maintained with a constant temperature of 22±5°C, 40-70% humidity and 12 h day-night cycle.The rats were fed with commercial laboratory pellet diet composition and water was supplied *ad libitum*. Standard rat pellet contained wheat (40%), wheat bran (20%), rice polishing (5%), fish

meal (10%), oil cake (10%), gram (3.9%), pulses (3.9%), milk (3.8%), soyabean oil (1.5%), molasses (0.95%), salt (0.95%) and vitamin (1%). The Guide of the Care and Use of Laboratory Animals (1996) was followed to perform the current study and this manuscript was prepared based on the ARRIVE Guidelines for reporting animal research (Kilkenny et al., 2010). The ethical clearance was attained from the ethical review committee of Bangladesh University of Health Sciences (BUHS) to conduct the study (Memo no: BUHS/ERC/EA/21/30) and according to the ethical review committee's suggestion regarding to reduce the sufferings of experimental animals all sorts of attempts were taken.

Preparation of type 2 diabetes model rats

A single intraperitoneal injection of STZ (prepared with citrate buffer , pH 4.5) was induced in 48 h old rat pups (average weight 7 g) at a dose of 90 mg/kg to develop nSTZ induced type 2 diabetic model as described by Bonner-Weir et al. (1981). After 3 months, STZ injected rat's diabetic status was checked by oral glucose tolerant test (OGTT) and considered them for the current study, those having fasting serum glucose level >7.00 mmol/L and at 2 h serum glucose level >14.00 mmol/L.

Dose and route of administration

For the evaluation of the anti-diabetic activity, the study materials were orally administered for consecutive 28 days with a single feeding. The grape seeds (OPC 95%) powder administrated at a dose of 1.25 g per 10 mL dd H_2O per kg body weight of T2DM model rats. As a positive control, the standard drug gliclazide was prepared at a dose of 20 mg per 5 ml of solvent (also added few drops of 0.1 N NaOH into the solution to dissolve gliclazide into water)/kg body weight of T2DM rat models and as a negative control, water was at a dose 10 ml/kg body weight.

Experimental design

A total of 18 type 2 diabetic model rats and 6 normal rats were used in this 28 days experimental period. The experimental rats were divided into 4 groups and every group contains six numbers of rats. These groups were represented as NWC (Normal water control), DWC (Diabetic water control), GT (Gliclazide treated) and GSP (Grape seeds powder) treated group.

Body weight measurement

The body weight of each rat was measured at seven days interval of the 28 days experimental period.

Collection of biological sample for biochemical analysis

Blood samples were collected from rats kept under fasting conditions by amputation of the tail tip under mild ether anesthesia at initial day. Just before the amputation, the tail was immersed into warm water (about 40°C) for approximately 30 to 40 s for vasodilatation. After cutting the tail tip, about 0.2 ml blood was taken cautiously in Eppendorf tube to avoid hemolysis. On the 28th day, after the animals were decapitated, their blood was collected from apex of the heart and liver was taken out, washed in ice-cold saline, and patted dry and processed for glycogen estimation. The collected blood samples were centrifuged at 3500 rpm for 15 min and finally the serum were separated into another Eppendorf tubes for biochemical analysis and 100 µL of serum were kept frozen at -20°C until analysis of fasting serum insulin.

Biochemical analysis

The following parameters of the experimented rats were measured for the anti-diabetic, lipidimic status and hepatic glycogen content of grape seeds powder.

(1) Serum glucose was measured by Glucose Oxidase (GOD-PAP) method using micro-plate reader (Bio-Tec, ELISA) (Kunst et al., 1984).
(2) Serum lipid profile [Total Cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) – cholesterol] was estimated by GOD-/PAP method in ELISA reader at 500 nm (Randox Laboratories LTD Ardmore, Diamond Road, Crumlin, Co. Antrim, United Kingdom BT294QY) (Wybenga Pileggi et al., 1970; Mcgown et al., 1983). Serum low density lipoprotein cholesterol (LDL-C) was calculated by the Fried Wald formula: LDL Cholesterol = Total Cholesterol – (1/5 TG + HDL Cholesterol).
(3) TG:HDL-C and TC:HDL-C was measured by the following calculation: TG:HDL-C= (TG/HDL-C) and TC:HDL-C=(TC/HDL-C) (Masson et al., 2016; Ballantyne, 2014),
(4) Measurement of glycogen from rat liver (Anthrone Sulfuric acid method) (Hassid et al.,1957),
(5) Serum insulin was measured by a rat insulin ELISA kit (Kratzsch et al., 1990).

Statistical analysis

Data were presented as mean ± standard deviation. Statistical analysis was done by using the Statistical Package for Social Science (SPSS) software for windows version 16 (SPSS Inc., USA). Analysis of variance (ANOVA, Bonferroni Post Test and Paired sample t-test) was done to see the difference between the groups and the initial day to postprandial day's difference. The level of significance was set at $p \leq 0.05$.

RESULTS

Effects of grape seeds powder (OPC 95%) treated on fasting serum glucose level of type 2 diabetic model rats

As depicted in Table 1, the initial fasting serum glucose level was (M±SD, mmol/L) 5.52±0.06, 8.92±0.54, 7.37±0.67, and 7.46±0.29 in NWC, DWC, GT and GSP treated rats, respectively where GSP treated group decreased FSG significantly ($p<0.009$) compared with baseline value [0 day vs 28 day: 7.46±0.29 vs 6.72±0.42 (M±SD, mmol/L)]. Moreover, a significant reduction ($p<0.001$) of glucose level was found when compared with the DWC group. As expected FSG level of diabetic water control rats were improved by 3% compared to base line value. As well as the FSG level of other two groups of rats decreased by 6% and 1% in gliclazide treated and NWC treated group, respectively.

Preliminary phytochemical analysis

Plant materials contain some chemical active constituents

Table 1. Fasting serum glucose level of type 2 diabetic model rats.

Group	Fasting serum glucose level (mmol/L)	
	0 day	28 day
NWC (n=6)	5.52±0.06 (100%)	5.48±0.04 (99%)
DWC (n=6)	8.92±0.54 (100%)	9.23±0.76 (103%)
GT (n=6)	7.37±0.67 (100%)	6.96±1.14 (94%)
GSP (n=6)	7.46±0.29 (100%)	6.72±0.24 (90%)*

Group NWC, DWC, GT, GSP represents normal water control, diabetic water control. Gliclazide treated and Grape seed powder treated diabetic rat respectively. Data presented as mean±standard deviation (M±SD). Statistical comparison between several groups was performed using one-way ANOVA and paired sample t test. *P<0.009.

Table 2. Phytochemical screening of Grape seed powder.

Phytochemical	Extract of grape seeds	Test
Alkaloids	-	Hager's test
Tannins	+ ++	Ferric-chloride solution
Phenols	+ + +	Potassium-Ferro-cyanide solution
Terpenoids	+ +	Salkowaski test
Saponins	+++	Froth test
Flavonoids	+ +	i) Mg ribbon test ii) Alkaline reagent test

(+) is present and (-) is absent.

which is responsible for the antidiabetic properties (Bharti et al., 2018). Table 2 shows some preliminary phytochemical tests such as alkaloids, tannins, phenols, terpinoids, saponins, and flavonoids.

In this present investigation, the phytochemical test has confirmed the presence of the high amount of tannins, phenols, saponins, terpenoids, flavonoids. On the other hand, alkaloids are absent in grape seed powder.

Effect of grape seeds powder on the body weight of T2DM rats

In 28 days experimental period, body weight of each rat was taken in every seven days interval. Initial body weight was NWC (183±5), DWC (168±18), GT (190±20) and GSP (182±3) treated groups (Table 3). The body weight of NWC, DWC, GT and GSP treated groups increased gradually as 36%, 27%, 12% and 22% respectively compared to their baseline value. However, comparing with NWC, DWC, GT and GSP treated group has shown a significant reduction ($p<0.006$, $p<0.007$, $p<0.002$ respectively) of their body weight at final day.

Effect of GSP lipid profiles on STZ-induced type 2 diabetic model rats

Chronic effects of GSP on serum lipid profiles are as shown in Figure 1a and 1b. Treatment with GSP showed a significant reduction of serum triglycerides and total cholesterol ($p<0.002$, $p<0.001$) when compared with base line value. Cholesterol level also significantly decreases ($p<0.001$) when compared with the DWC treated group rats. The triglycerides and total cholesterol levels were decreased in GT group by 16% and 10%, respectively when compared with their initial day. LDL level was also significantly ($p<0.05$) decreased in GSP treated group (4% and 9%) where HDL increased in GT and GSP (6% and 4%), respectively on final day compared to base line value.

After 28 days experimental period, GSP treated rats improve the TG: HDL and TC: HDL ratio which is shown in Table 4. At the end of the experiment, the ratio lied between (M±SD) 3.50±0.11 to 2.62±0.25 and 2.84±0.21 to 2.15 ±0.22, respectively. Both ratio of TG: HDL-C significantly ($p<0.004$) ($P<0.01$) decreased when compared with the initial day vs final day. On the other hand, GT treated group also showed reduction of TG: HDL-C ratio (up to 21-16%).

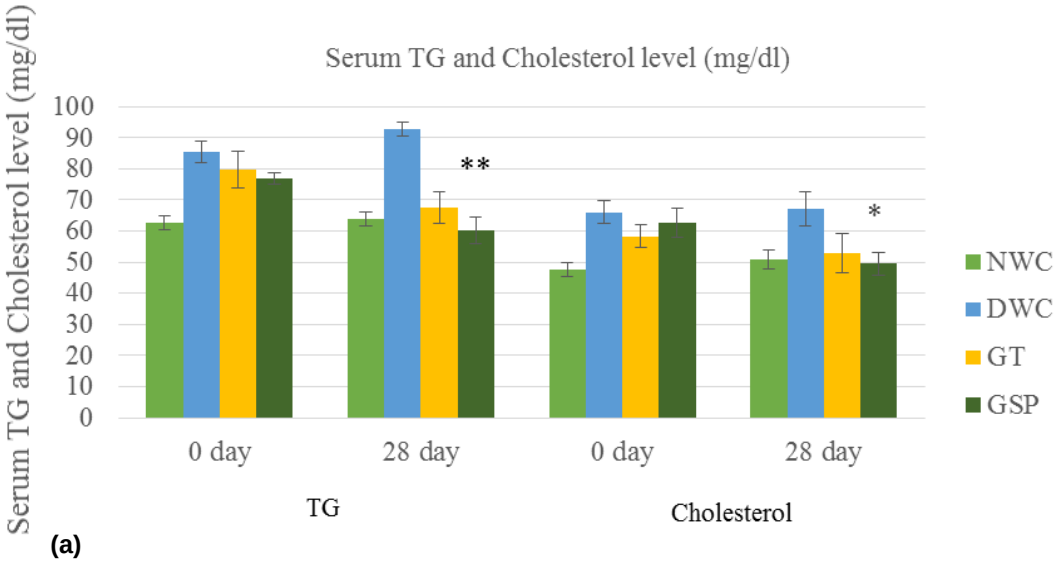
Effects of GSP on the liver glycogen of type-2 diabetic model rats

After 28 days of experimental period, all rats were sacrificed and their hepatic glycogen level measured.

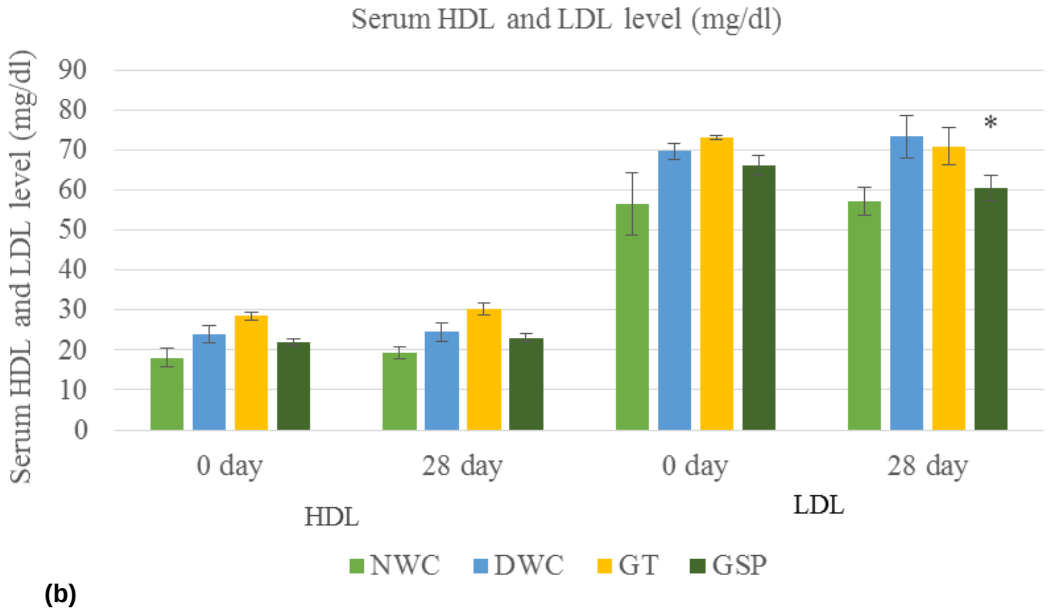
Table 3. Determinations of the effect of GSP on Body weight on STZ induced diabetic rats and normal rats.

Group	Body weight (gm)				
	0 day	7 days	14 days	21 days	28 days
NWC (n=6)	183±5 (100%)	195±7	221±11	225±10	249±11 (136%)
DWC (n=6)	168±18 (100%)	196±19	206±18	214±17	214±17 (127%)
GT (n=6)	190±20 (100%)	196±14	200±22	212±21	214±24 (112%)
GSP (n=6)	182±3 (100%)	177±3	187±3	190±6	206±1 (113%)

Group NWC, DWC, GT, GSP, represents normal water control, diabetic water control and gliclazide treated and grape seed powder treated diabetic rat respectively. Data presented as mean ± standard deviation (M±SD).



(a)



(b)

Figure 1. (a) Effects of grape seed powder treated rats on triglycerides and cholesterol level (0 day to 28 day), **p<0.002, *p<0.001. (b) Effects of grape seeds powder treated rats on HDL and LDL level (0 day to 28 day), *p<0.05.

Table 4. Effects of GSP treated on triglycerides to HDL-C ratio and total cholesterol to HDL-C

Groups	TG: HDL-C		TC: HDL-C	
	0 day	28 day	0 day	28 day
NWC (n=6)	3.51±0.40 (100%)	3.34±0.29 (95%)	2.21±1.16 (100%	2.24±1.12 (101%)
DWC (n=6)	3.07±1.53 (100%)	3.17±1.61 (103%)	2.77±0.16 (100%)	2.76±0.38 (99%)
GT (n=6)	2.80±0.23 (100%)	2.22±0.15 (79%)	2.05±0.18 (100%)	1.74±0.19 (84%)
GSP (n=6)	3.50±0.11 (100%)	2.62±0.25 (74%)**	2.84±0.21 (100%)	2.15±0.22 (75%)*

Group NWC, DWC, GT, GSP, represents normal water control, diabetic water control, and gliclazide treated and grape seed powder treated diabetic rat, respectively. Data presented as (M±SD). Statistical comparison between groups was performed using one-way ANOVA and paired sample t-test. **p<0.004, *p<0.01.

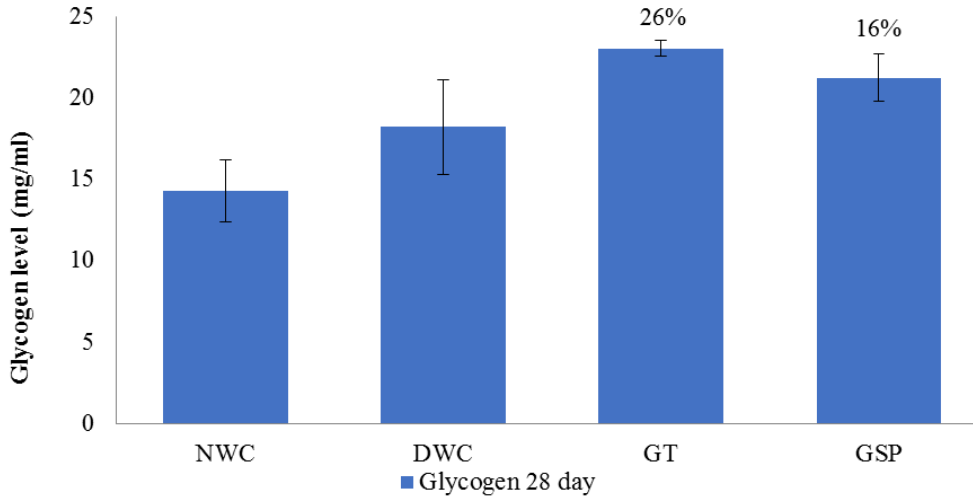


Figure 2. Effects of grape seeds powder treated rats on glycogen level (28-day). Data presented as (M±SD).

Figure 2 shows chronic effects of GSP on hepatic glycogen content of type 2 diabetic model rats and normal rats. Hepatic glycogen content in gliclazide and GSP were found to increase by 26% and 16% respectively on final day of the experiment in comparison with DWC.

Chronic effects of grape seed powder on insulinemic status of type-2 diabetic model rats

A significant (p<0.001) increment of insulin level was observed in GSP treated group compared with baseline value (Figure 3). In case of other groups, the gliclazide treated group and normal water control group, the serum insulin level was found to be increased by 29% wherein DWC group, the serum insulin level decreased by 32%.

DISCUSSION

The incidence of diabetes is increasing throughout the world so rapidly that it has become one of the most challenging public health problem of the 21st century (Tabish, 2007). Although enormous progress has been made in the therapeutic management of type 2 diabetes; however, the available antidiabetic drugs still suffer from severe limitations including safety, tolerability, hypoglycemia, lactic acidosis, weight gain and gastrointestinal disturbances (Chaudhury et al., 2017). Medicinal plants used to treat hypoglycemic and antihyperglycemic conditions are of considerable interest as they are recognized to contain valuable medicinal properties in different parts of the plant (Babu et al., 2006).

The present study was undertaken to screen the phytochemical constituents and to investigate the effect of GSP on serum glucose, serum lipids, serum insulin, body weight and liver glycogen contents of type 2 diabetic model rats after 28 days consecutive feeding. As mentioned earlier, in the present study, type 2 diabetes mellitus was induced by injecting STZ to 48 h old pups and experiments were carried out three months later by confirming diabetes through oral glucose tolerance test.

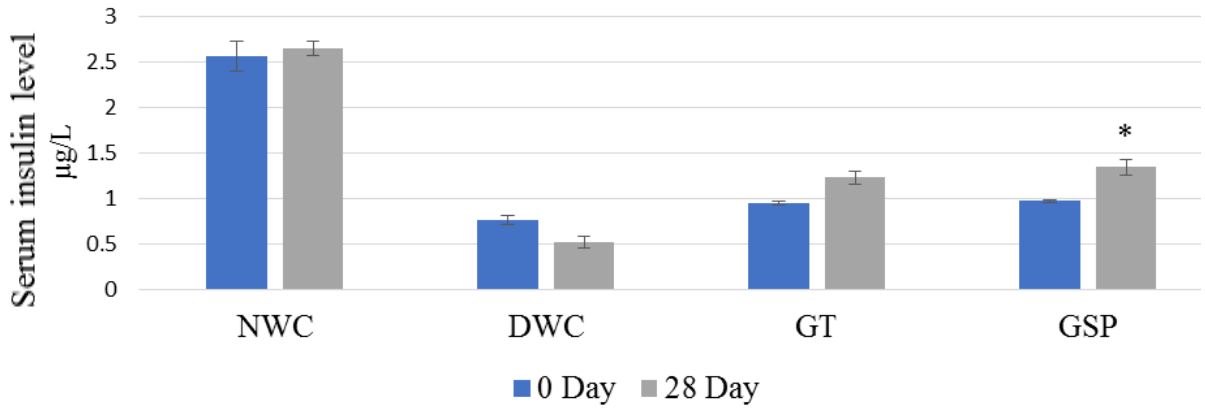


Figure 3. Effects of GSP on the insulin-memetic status of type-2 diabetic model rats. Data presented as mean ± standard deviation (M±SD). *P<0.001.

This method induces diabetic syndrome with reduced pancreatic insulin stores that mimic some features of type 2 diabetes. Streptozotocin selectively destroys β-cells leading to a reduction of insulin release and induced hyperglycemia (Palmer et al., 1998; Hossain et al., 2020). Decrease in insulin release could result in impaired glucose regulation by suppressing hepatic glucose production and reduction of glucose uptake in insulin sensitive tissues. Gliclazide was used as a standard drug for type 2 diabetic rats which act mainly by augmenting insulin secretion.

In this chronic study, serum glucose level was measured on 0 day and 28th days of the experiment. A significant decrease in the fasting serum glucose level was found on 28th day in GSP treated group (P=0.009) (Table 1) compared with 0 day and when compared with the diabetic water control (p=0.001). Other groups showed non-significant decrease in blood glucose level after chronic treatment. This observation was also supported by the Pinent et al. (2004) report who claimed that grape seed extract exhibits pronounced antidiabetic properties in STZ induced diabetic rats (Pinent et al., 2004).

The phytochemical screening revealed the presence of a number of phytochemicals in GSP like tannins, phenols, saponins, terpenoids and flavonoids (Table 2). Existing scientific data supports the present findings that *Vitis vinifera* L. (grape) seed contains essential phytochemicals (tannins, phenols, flavonoids, saponins, terpenoids) that are crucial for glucose homeostasis (Unusan, 2020). Therefore, the obtained hypoglycemic effect may be due to the presence of phytochemicals in GSP.

It was explored whether the blood glucose lowering effect was due to reduction of food intake. This was done by comparing the body weight between the control and treated groups. The result showed that there was a non-significant increase of body weight in both control and treated (GSP and gliclazide) groups (Table 3). The gain in body weight was of similar proportion in the control and treated groups and thus they do not explain the hypoglycemic effect in the extract group. The findings also suggest that GSP (OPC 95%) does not alter normal metabolic parameters like food and water intake.

In order to know the probable mechanism of hypoglycemic effect after chronic treatment of GSP the serum insulin level of type 2 diabetic rats was measured at the beginning and after 28 days. A significant increase (p<0.001) of insulin was observed in GSP treated groups at the end of the study (Figure 3) which might contribute in reducing fasting serum glucose level in the corresponding group.

Furthermore, liver glycogen estimate demonstrated a stimulatory impact on hepatic glycogenesis, which might be the cause of the blood glucose reduction (Bhowmik et al., 2009). Montagut et al. (2010) discovered that the insulin-mimetic characteristics of grape seed oligomers procyanidin extract increased cellular glucose absorption in insulin-sensitive L6E9 and 3T3L1 cell lines (Montagut et al., 2010). In our results, oligomeric proanthocyanidin GSP (OPC 95%) may have the potential to store glucose via hepatic glycogen synthesis (glucogenesis) as well as enhance cellular glucose absorption insulin sensitivity cells via phosphorylation of insulin receptors (Yogalakshmi et al., 2014). This may be another possibility of GSP to regulate the serum glucose level in type 2 diabetic model rats.

Type 2 diabetes is associated with marked imbalance in lipid metabolism (Gadi and Samaha, 2007). Diabetic dyslipidemia is characterized by low level of HDL-cholesterol and elevated level of total cholesterol, triglycerides and LDL-cholesterol. The association of hyperglycemia 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 reduction of micro- and macro vascular diseases in individuals with

type 2 diabetes (UKPDS, 1998). Hence, improvement in the lipid abnormalities must play beneficial role in inhibiting the complications of diabetes. The present study (Figure 1a and 1b) revealed that grape seed powder treated groups significantly reduced (P<0.002) triglycerides level as well as total cholesterol level (P<0.01) when compared with the baseline value. LDL levels also significantly decreased (p<0.05) and HDL levels also improved (4%). According to Vega Vargas et al. (2017), grape seed have vasodilator effects that help to enhance lipid profile levels and reduce LDL oxidation, both of which help to reduce cardiovascular disease, this supports the existing findings (Vega Vargas et al., 2017). Phenolic compounds of Grape seed may have the possibility that reduce several risk factors connected with cardiovascular disease, and procyanidins may cause a rise in HDL and a drop in LDL levels (Preuss et al., 2000; Vinson et al., 2002; Auger et al., 2004; Caimari et al., 2013). Moreover, the ratio of the TG: HDL (p<0.004) and Cholesterol: HDL (p<0.01) level was significantly decreased at the end of the experiment (Table 4). The ratio of triglycerides to HDL and Cholesterol to HDL lied between 1 and 3 where it was reported that the ratio TG:HDL is more than 4 and TC:HDL ratio is more than 5 are the most powerful predictor of coronary heart disease development (Ali et al., 2020; Luz et al., 2008; Bleda et al., 2012). Thus, this finding strongly suggests that grape seed powder (OPC 95%) possesses hypoglycemic and lipid-lowering properties.

Conclusion

The findings of the present study suggest that GSP was effective in reducing the glycemic status of type 2 diabetic rats and therefore possesses significant hypoglycemic properties. It also improves dyslipidemia by lowering atherogenic lipids and by increasing HDL-cholesterol level also by decreasing the TG: HDL ratio, Cholesterol: HDL ratio level. The probable mechanism maybe, as insulino mimetic mediated through the glycolytic pathway and also reduce the glucose level via increasing the serum insulin level. Therefore, further in-depth studies are needed to explore the exact mechanism of GSP in regulating glucose homeostasis for the development of novel antidiabetic drug from GSP in future.

ABBREVIATIONS

OGTT, Oral glucose tolerance test; **GT,** gliclazide treated; **GSP,** grape seeds powder; **OPC 95%,** oligomeric proanthocyanidins 95%; **DWC,** diabetic water control; **NWC,** normal water control; **STZ,** streptozotocin; **TG,** triglycerides; **HDL,** high density lipoprotein; **LDL,** Low density lipoprotein; **AMPK,** AMP-activated protein kinase; **GSE,** grape seed extract; **IDF,** International Diabetic Federation; **GLUT-4,** glucose transporter type 4; **IFG,** impaired fasting glucose; **IGT,** impaired glucose tolerance.

CONFLICT OF INTERESTS

The authors have not declared any conflict of conflict of interests.

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