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Original article

Ameliorative property of *Sesbania grandiflora* on carbohydrate metabolic enzymes in the liver and kidney of streptozotocin-induced diabetic rats

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ABSTRACT

In diabetic condition, endogenous glucose synthesis will be elevated due to defect in the action of vital enzymes involved in carbohydrate metabolism, which is the main cause for hyperglycemia. The current study was designed to explore the anti-hyperglycemic efficacy of *Sesbania grandiflora* flower (SGF) extract by evaluating the concentration of C-peptide, insulin, glucose, glycosylated hemoglobin (HbA_{1C}), hemoglobin (Hb), glycogen and carbohydrate metabolic enzymes activities in diabetic rats. The study found to lower the level of glucose, HbA_{1C} and simultaneously ameliorated concentrations of C-peptide, insulin, hemoglobin (Hb), glycogen and carbohydrate metabolic enzymes activities in SGF treated (250 mg/kg body weight for 45 days) diabetic rats. Moreover, SGF administered diabetic rats showed diminished consumption of food and water at the same time improved body weight. The results obtained from the present study were compared with glibenclamide treated (600 μg/kg body weight) diabetic rats. SGF were supplemented to normal rats to rule out toxic effect of SGF, to explore any significant alteration in the above parameters. Hence, the results depict that SGF modulated the carbohydrate metabolic enzymes activities through ameliorating the secretion of insulin and diminishing the level of glucose concentration in STZ-induced diabetic rats by its bioactive compounds.

1. Introduction

Carbohydrate, protein and lipid metabolic defects causes diabetes mellitus. To regulate these metabolic activities insulin is very essential. Due to defect in secretion or action of insulin, the blood glucose level has elevated that is specific sign of diabetes mellitus. (Al-Attar and Alsalmi, 2019; Jiang et al., 2020a, 2020b, 2020c). Increased blood glucose damages the proteins, lipids and nucleic acids of the cells by elevated abnormal glucose metabolic products which are the key player of diabetic complications (Laxy et al., 2021). The prolonged hyperglycemia of diabetes mellitus is linked with many organ damage and dysfunction like nerves, eyes, blood vessels, heart, liver, kidneys and testis (Maresch et al., 2018). To protect all organ systems from diabetes, people should follow proper management system to prevent diabetes mellitus and reduce the risk of diabetes associated complications. Many epidemiological studies and clinical research reports are strongly insisting that prolonged diabetic complications are caused by chronic hyperglycemia, it activates glucose auto-oxidation, protein glycation and stimulates polyol metabolism (Chitra et al., 2020). Based on the report of International Diabetes Federation, 463 million people affected by diabetes in 2019. This might rise to 578 mil-

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lion people by the year of 2030 and 700 million people by the year of 2045. The uncontrolled elevation of diabetes might be due to consumption of junk food or high fat content food, obesity, sedentary lifestyle, etc.

Fasting and postprandial blood glucose level of normal subjects should be maintained at a particular range. The blood glucose homeostasis is balanced by exogenous glucose obtained from the food and endogenous glucose synthesized by the tissues like liver and kidney, consumption of glucose by various tissues, while excess glucose will be converted into glycogen and stored in the tissues (Jiang et al., 2020a, 2020b, 2020c). Liver plays a vital function to maintain the normal range of blood glucose concentration along with the kidneys playing minor part in the process of regulation of blood glucose. To control the blood glucose concentration within the normal range many metabolic pathways are involving mainly glycogenolysis, gluconeogenesis, glycolysis and glycogenesis (Hanhineva et al., 2010; Jiang et al., 2020a, 2020b). When blood glucose level decreased below normal, glycogenolysis and gluconeogenesis pathway enzymes will be regulated to produce glucose. If blood glucose level is elevated above normal, the glycolysis and glycogenesis process will be activated to maintain the blood glucose homeostasis. There are many enzymes and substrates that are involved in the process of carbohydrate metabolic pathways which are regulated by endocrine system. If any defect occurs in endocrine system that leads alteration in carbohydrate metabolic pathways which causes diabetes (Hanhineva et al., 2010; Jiang et al., 2020a, 2020b).

The main task of diabetes management is to control the blood glucose concentration within the normal range. Numerous antidiabetic drugs are commercially available, but these drugs give many adverse effects like gastrointestinal disturbances, diarrhea, lactic acidosis, hepatotoxicity, weight gain and sever hypoglycemia after prolonged treatment (Chaudhury et al., 2017). To treat diabetic patients without any adverse effects is a challenging task in health care system. Therefore, many new drug development researchers are concentrating to develop antidiabetic drugs without any adverse effects from natural compound derived from medicinal plants.

Sesbania grandiflora (SG) is commonly applied to treat various diseases in the traditional medicine. All parts of this plant possess numerous pharmacological properties like hypolipidemic, hepatoprotective, renal protective, broncho protective, cardio protective, neuroprotective etc., (Ramesh and Hazeena Begum, 2006, 2008; Ramesh et al., 2007a, 2007b, 2008, 2010, 2015a, 2015b). The flowers of SG are used to treat night blindness, headache, nasal catarrh, phthisis and amenorrhea. SG flower (SGF) contains several bioactive compounds such as flavonoids, terpenoids, triterpenes, anthocyanin, saponins, phenolics, alkaloids, tannins, ascorbic acid and β-carotene (Loganayaki et al., 2012; Andarwulan et al., 2012; Dethe et al., 2014). Previous reports illustrate that SGF extract has anti-nociceptive, anticancer, anti-inflammatory, antioxidant and antimicrobial properties (Loganayaki et al., 2012; Sreelatha et al., 2011; China et al., 2012). Boonmee et al. (2007) demonstrated the antidiabetic property of SGF by inhibiting α-glucosidase activity. Our previous study reported that SGF diminished oxidative stress in the erythrocytes of diabetic rats (Sureka et al., 2015). However, the detailed mechanism of action of SGF is not clearly illustrated in diabetic rats. According to the literatures, there is no studies reported the effects of SGF in blood glucose homeostasis through regulation of enzymes action in the metabolism of carbohydrate in STZ-induced diabetic rats. Hence, the current study was planned to explore the antihyperglycemic efficacy of SGF by analyzing the enzymes action which regulate the metabolism of carbohydrate in the liver and kidney tissues of diabetic rats and the potency of SGF was compared with glibenclamide.

2. Materials and methods

2.1. Chemicals

Glibenclamide (Glib) and Streptozotocin (STZ) were procured from Sigma–Aldrich, USA. Most of the reagents, solvents, chemicals with high purity and its grade was analytical got from Himedia Chemicals, India. All chemicals were stored in appropriate temperature.

2.2. Plant materials

Sesbania grandiflora flowers (SGF) were plucked as fresh from the plant located in the farm at Thanjavur district, Tamil Nadu, India. Fresh flowers were dried meticulously under shade and ground as fine powder. This SGF powder was packed in an airtight container and used for the extract preparation.

2.3. Preparation of extracts

First, lipid content and pigments were removed from SGF (500 g) powder by using 2.5 L petroleum ether (1:5 w/v). The petroleum ether extract was dried at 40 °C by using a hot air oven and then further extracted by using methanol through Soxhlet extraction method. The extraction solvent was removed with the help of rotary vacuum-evaporator at 50 °C and then lyophilized to remove the water content. This lyophilized extract was dissolved in 1% sodium carboxy methyl cellulose (SCMC). The 1% SCMC used as vehicle for this experiment.

2.4. Animals

This experiment was setup in Wistar strain male albino rats with 190–220 g of body weight (b. wt). The rats were maintained in polypropylene cages at 25 ± 2 °C with 12-hours light and 12-hours dark cycle. The humidity of the room was 50% and the rats were allowed freely to have rat feed and drinking water. The animal experimental procedures were followed by the animal ethical guidelines approved by the Ethical Committee, Tamil University, Thanjavur, Tamil Nadu, India.

2.5. Induction of experimental diabetes

STZ was prepared in citrate buffer (0.1 M, pH 4.5) and administered to rats *via* intra peritoneal injection (single dose, 45 mg/kg b. wt) after 12 h fast. 20% glucose solution was given to STZ injected rats to avoid STZ induced initial hypoglycemic mortality. After 48 h, blood glucose was assessed in the STZ injected rats. For this experiment, diabetic rats were selected based on the plasma glucose concentration 200–300 mg/dL.

2.6. Oral glucose tolerance test (OGTT)

OGTT was assessed followed by the protocol of Zhang et al. (2008). After 12 h fasting, blood was drawn from the rats of all groups were consider as 0 min and then glucose solution (2 g/kg b. wt) was given orally. After 30, 60, 90 and 120-minutes interval, blood was drained from the retro orbital sinus of glucose administered control and experimental rats. The blood drawn with sodium fluoride and potassium oxalate solution containing tube and glucose concentration was assessed in all the group of rats.

2.7. Experimental design

Rats were assigned into five groups and six rats per group as given below. Normal and diabetic control rats received only vehi-

cle, SGF and glibenclamide (Glib) were administered to experimental rats, single dose per day for 45 days.

Group I	Normal control (NC) received only vehicle
Group II	Normal rats received SGF (N + SGF, 250 mg/kg b. wt)
Group III	Diabetic control (DC) received only vehicle
Group IV	Diabetic rats received SGF (D + SGF, 250 mg/kg b. wt)
Group V	Diabetic rats received Glib (D + Glib, 600 μg/kg b. wt)

All the group of rats' glucose concentration, consumption of food and water quantity and changes of body weight were assessed during the experimental periods at regular intervals. After 45 days, all the group of rats were made overnight fast and sacrificed in anesthetic (intramuscular injection of ketamine 24 mg/kg b. wt) condition. Blood was drained in collection tubes with and without anticoagulant. Liver and kidney were dissected immediately, washed to remove blood in ice-cold saline and 10% homogenate was prepared by using Tris-HCl buffer (0.1 M, pH 7.4) and centrifuged (1000 × g for 10 min). The separated supernatants were used to assess biochemical parameters.

2.8. Biochemical analysis

Glucose level was assessed by glucose assay kit based on the procedure of Trinder (1969). C-peptide and insulin concentration were quantified by ELISA kit (Boeheringer, Mannheim). Amount of hemoglobin (Hb) and glycosylated hemoglobin (HbA_{1C}) were quantified by the procedures of Drabkin and Austin (1932) and SudhakarNayak and Pattabiraman (1981). The activity of hexokinase (HK) was determined by the protocol of Brandstrup et al. (1957). The potency of pyruvate kinase (PK) activity was assessed according to the protocol of Pogson and Denton (1967). The performance of lactate dehydrogenase (LDH) activity was determined by the procedure of King (1959). The activity of fructose-1,6-bisphosphatase (F1,6BP) was assessed based on the protocol of Gancedo and Gancedo (1971). The activity of glucose-6-phosphatase (G6Pase) was investigated followed by the protocol of Koide and Oda (1959). The performance of glucose-6-phosphate dehydrogenase (G6PDH) activity was measured according to the protocol of Ells and Kirkman (1961). The activity of glycogen phosphorylase (GP) was assessed by the protocol of Cornblath et al. (1963). The efficacy of glycogen synthase (GS) activity was determined based on the procedure of Leloir and Goldemberg (1962). The amount of glycogen was quantified followed by the procedure of Morales et al. (1973).

2.9. Statistical analysis

All the experimental results were showed as mean ± S.D (n = 6). Statistical significances were investigated by ANOVA followed by Tukey's multiple comparison (post-hoc test) using a software (Graphpad prism, Version 5.0). $P < 0.05$ was fixed as statistically significant.

3. Results

3.1. Effect of SGF on plasma glucose and insulin levels

Glucose and insulin concentration of plasma were observed in the experimental rats and normal control rats after 48 h then at 7th, 15th, 30th and 45th day of SGF treatment (Tables 1 and 2). In the plasma of diabetic rats, insulin concentration was diminished and glucose concentration was raised markedly ($P < 0.001$). After supplementation of SGF, insulin concentration was raised and glucose was reduced markedly ($P < 0.001$) in the plasma of diabetic rats. The effect of SGF after 48 h of treatment did not show any significant difference, a marked antihyperglycemic effect was observed from 7th day onwards. A marked reduction of glucose concentration in plasma was observed on 30th day of SGF treatment. The experimental period was further increased up to 45 days, a marked reduction of glucose and elevation of insulin was found in the plasma. The results of glucose and insulin concentrations were found in the plasma of diabetic rats treated with Glib are almost similar with SGF treated diabetic rats.

3.2. Effect of SGF on oral glucose tolerance test

Glucose concentration was assessed in the plasma of normal and diabetic control rats, SGF and Glib treated diabetic rats after ingestion of oral glucose solution (2 g/kg b. wt) was shown in Table 3. Glucose concentration reached a peak in diabetic rats after 60 min of glucose ingestion. The glucose concentration was slightly started to decrease even though it was continuously at high concentration after 120 min. After 60 and 120 min of oral glucose ingestion, the concentration of glucose was significantly decreased in the plasma of SGF and Glib treated diabetic rats. The concentration of glucose was significantly reduced more at 120 min when compared with 30 and 60 min in the plasma of SGF treated normal control rats.

3.3. Effect of SGF on body weight changes, food and water consumption

Changes of body weight, quantity of food and water consumed by rats of experimental and control groups were presented in Table 4. Significantly high ($P < 0.001$) amount of food and water ingested by diabetic rats and marked reduction ($P < 0.001$) of body weight was observed in diabetic rats. SGF and Glib treatment was dropped the ingestion of food and water whereas ameliorated the body weight of diabetic rats. There is no change in food and water ingestion and body weight of normal control rats treated with SGF.

3.4. Effect of SGF on the levels of C-peptide, Hb and HbA_{1C}

Changes of C-peptide, Hb and HbA_{1C} concentrations were measured in the rats of experimental and control groups and expressed in Table 5. Remarkable decrease ($P < 0.001$) in the concentrations of C-peptide and Hb were noticed at the same time elevated ($P < 0.001$) concentration of HbA_{1C} was found in diabetic rats. The changes of C-peptide, Hb and HbA_{1C} concentrations were reverted to normal range in SGF and Glib treated diabetic rats. When SGF treated with normal control rats did not make any marked alterations in C-peptide, Hb and HbA_{1C} concentrations.

3.5. Effect of SGF on the activities of HK, PK and LDH

Changes of HK, PK and LDH activities were assessed in the liver and kidney of experimental and control group rats and illustrated in Figs. 1 and 2. The diabetic rat liver and kidney were depicted a marked ($P < 0.001$) reduction in HK and PK activities and a marked ($P < 0.001$) elevation in LDH activity. The changes of HK, PK and LDH activities were reverted to normal range in the liver and kidney of SGF and Glib treated diabetic rats. When SGF treated with normal control rats did not illustrate any marked differences in HK, PK and LDH activities.

Table 1
Effect of SGF on plasma glucose in normal and diabetic rats.

Groups	Plasma glucose (mg/dL)					
	0 days	48 h after STZ-injection	7 days	15 days	30 days	45 days
Normal control	77.20 ± 3.13	78.66 ± 6.53	77.50 ± 7.79	81.16 ± 7.14	80.81 ± 5.42	79.65 ± 4.08
Normal + SGF (250 mg/kg b.wt)	77.83 ± 4.79	77.00 ± 5.65^{aNS}	78.16 ± 4.40^{aNS}	75.83 ± 4.79^{aNS}	74.67 ± 5.43^{aNS}	72.00 ± 6.66^{aNS}
Diabetic control	80.67 ± 5.57	263.00 ± 11.57^{a*}	272.17 ± 13.01^{a*}	294.33 ± 10.89^{a*}	316.17 ± 13.09^{a*}	337.50 ± 12.01^{a*}
Diabetic + SGF (250 mg/kg b.wt)	78.33 ± 5.13	245.33 ± 8.82^{bNS}	217.50 ± 14.33^{b*}	202.82 ± 6.97^{b*}	141.50 ± 10.63^{b*}	98.50 ± 6.75^{b*}
Diabetic + Glib (600 μg/kg b.wt)	76.00 ± 3.03	248.50 ± 11.24^{bNS}	218.82 ± 14.48^{b*}	201.30 ± 5.47^{b*}	117.50 ± 7.79^{b*}	92.83 ± 6.62^{b*}

Values are illustrated as mean ± SD; n = 6 per group. Statistical comparisons "a" compared with normal control, "b" compared with diabetic control. *represent significance at $p < 0.001$, ^{NS} represent non-significant.

Table 2
Effect of SGF on plasma insulin in normal and diabetic rats.

Groups	Plasma insulin (μU/mL)					
	0 days	48 h after STZ-injection	7 days	15 days	30 days	45 days
Normal control	16.50 ± 1.64	16.16 ± 1.20	16.20 ± 1.17	16.33 ± 1.03	16.15 ± 0.75	16.20 ± 1.32
Normal + SGF (250 mg/kg b.wt)	15.67 ± 0.52	15.50 ± 0.54^{aNS}	15.83 ± 0.75^{aNS}	15.66 ± 0.81^{aNS}	15.75 ± 0.42^{aNS}	15.83 ± 0.68^{aNS}
Diabetic control	16.17 ± 1.16	5.65 ± 0.76^{a*}	5.26 ± 0.73^{a*}	5.10 ± 0.46^{a*}	4.94 ± 0.38^{a*}	4.81 ± 0.41^{a*}
Diabetic + SGF (250 mg/kg b.wt)	17.32 ± 1.03	6.45 ± 0.50^{bNS}	6.23 ± 0.22^{bNS}	6.81 ± 0.40^{b*}	6.85 ± 0.49^{b*}	7.59 ± 0.38^{b*}
Diabetic + Glib (600 μg/kg b.wt)	15.67 ± 1.21	5.00 ± 0.27^{bNS}	5.12 ± 0.45^{bNS}	6.57 ± 0.46$^{b€}$	6.61 ± 0.21^{b*}	7.88 ± 0.18^{b*}

Values are illustrated as mean ± SD; n = 6 per group. Statistical comparisons "a" compared with normal control, "b" compared with diabetic control. $^{*, €}$ represent significance at $p < 0.001$, $p < 0.01$, ^{NS} represent non-significant.

Table 3
Effect of SGF on oral glucose tolerance test in normal and diabetic rats.

Groups	Plasma glucose (mg/dl)				
	0 min	30 min	60 min	90 min	120 min
Normal control	80.50 ± 7.44	163.33 ± 12.54	144.83 ± 8.95	107.83 ± 7.94	83.60 ± 6.37
Normal + SGF (250 mg/kg b.wt)	79.11 ± 5.66^{aNS}	163.75 ± 9.22^{aNS}	141.17 ± 10.91^{aNS}	102.83 ± 5.84^{aNS}	81.50 ± 4.68^{aNS}
Diabetic control	262.42 ± 15.09^{a*}	334.59 ± 24.54^{a*}	386.17 ± 22.83^{a*}	364.33 ± 19.98^{a*}	323.83 ± 22.66^{a*}
Diabetic + SGF (250 mg/kg b.wt)	108.52 ± 4.05^{b*}	192.40 ± 10.31^{b*}	170.54 ± 8.69^{b*}	138.50 ± 7.18^{b*}	111.58 ± 8.31^{b*}
Diabetic + Glib (600 μg/kg b.wt)	99.01 ± 6.29^{b*}	191.15 ± 10.07^{b*}	169.13 ± 4.85^{b*}	128.17 ± 6.11^{b*}	107.67 ± 7.79^{b*}

Values are illustrated as mean ± SD; n = 6 per group. Statistical comparisons "a" compared with normal control, "b" compared with diabetic control. * represent significance at $p < 0.001$, ^{NS} represent non-significant.

Table 4
Effect of SGF on body weight, food and water intake in normal and diabetic rats.

Groups	Body weight (g)		Water intake (ml/rat/day)		Food intake (g/rat/day)	
	Initial	Final	Before	After	Before	After
Normal control	190.00 ± 5.18	219.32 ± 5.96	78.17 ± 3.97	76.20 ± 4.17	18.50 ± 1.05	18.16 ± 1.94
Normal + SGF (250 mg/kg b.wt)	192.83 ± 4.75	221.50 ± 4.59^{aNS}	79.83 ± 5.60	82.67 ± 4.13^{aNS}	18.67 ± 1.37	17.92 ± 1.20^{aNS}
Diabetic control	192.33 ± 5.43	148.30 ± 6.71^{a*}	153.16 ± 10.63	168.50 ± 13.31^{a*}	51.50 ± 3.56	68.50 ± 6.28^{a*}
Diabetic + SGF (250 mg/kg b.wt)	191.67 ± 6.89	204.83 ± 6.08^{b*}	121.00 ± 7.24	97.16 ± 8.21^{b*}	38.82 ± 3.54	29.67 ± 2.07^{b*}
Diabetic + Glib (600 μg/kg b.wt)	190.50 ± 4.97	208.50 ± 4.97^{b*}	120.50 ± 10.65	98.33 ± 7.28^{b*}	40.50 ± 2.59	29.82 ± 3.06^{b*}

Values are illustrated as mean ± SD; n = 6 per group. Statistical comparisons "a" compared with normal control, "b" compared with diabetic control. * represent significance at $p < 0.001$, ^{NS} represent non-significant.

Table 5
Effect of SGF on the levels of C-peptide, Hb and HbA_{1C} in normal and diabetic rats.

Group	Normal control	Normal + SGF (250 mg/kg b.wt)	Diabetic control	Diabetic + SGF (250 mg/kg b.wt)	Diabetic + Glib (600 μg/kg b.wt)
C-peptide	21.53 ± 1.97	22.62 ± 2.13^{aNS}	11.13 ± 0.82^{a*}	19.85 ± 1.69^{b*}	20.43 ± 1.86^{b*}
Hb (g/dL)	13.32 ± 0.72	13.89 ± 1.08^{aNS}	8.30 ± 0.62^{a*}	12.22 ± 0.82^{b*}	12.58 ± 1.04^{b*}
HbA_{1C} (mg/gHb)	0.41 ± 0.03	0.42 ± 0.03^{aNS}	1.05 ± 0.06^{a*}	0.65 ± 0.05^{b*}	0.61 ± 0.03^{b*}

Values are illustrated as mean ± SD; n = 6 per group. Statistical comparisons "a" compared with normal control, "b" compared with diabetic control. * represent significance at $p < 0.001$, ^{NS} represent non-significant.

3.6. Effect of SGF on the activities of G6Pase, F1,6BP and G6PDH

Changes of G6Pase, F1,6BP and G6PDH activities were investigated in the liver and kidney of experimental and control group rats and demonstrated in Figs. 3 and 4. The diabetic rat liver and kidney were showed a marked ($P < 0.001$) elevation in G6Pase and F1,6BP activities and a marked ($P < 0.001$) diminution in G6PDH activity. The alterations of G6Pase, F1,6BP and G6PDH activities returned to normal level in the liver and kidney of SGF and Glib treated diabetic rats. When SGF treated with normal con-

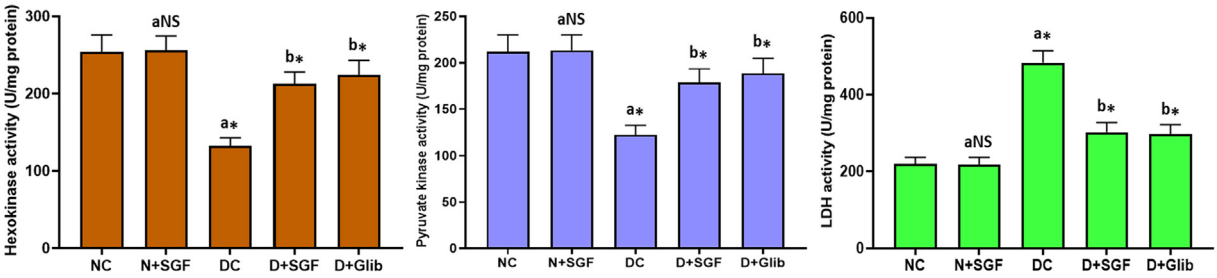

Fig. 1. Change of Hexokinase (HK), Pyruvate kinase (PK) and Lactate dehydrogenase (LDH) activities in the liver of control and experimental rats. The units of enzymes activity were expressed as HK - μM of glucose-6-phosphate generated/h/mg protein, PK - μM of pyruvate generated/min/mg protein and LDH - μM of pyruvate generated/h/mg protein. The results were expressed as mean ± SD (n = 6). The experimental groups were statistically compared as "a" DC and N + SGF versus NC, "b" D + SGF and D + Glib verses DC. *$p < 0.001$, NS: non-significant.

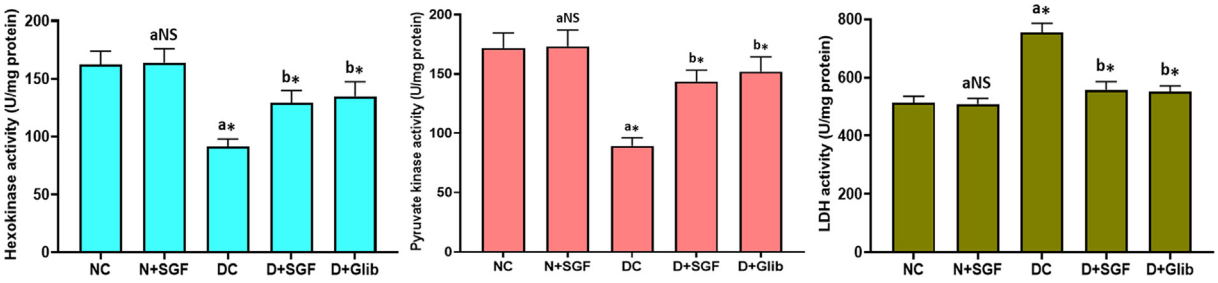

Fig. 2. Change of Hexokinase (HK), Pyruvate kinase (PK) and Lactate dehydrogenase (LDH) activities in the kidney of control and experimental rats. The units of enzymes activity were expressed as HK - μM of glucose-6-phosphate generated/h/mg protein, PK - μM of pyruvate generated/min/mg protein and LDH - μM of pyruvate generated/h/mg protein. The results were expressed as mean ± SD (n = 6). The experimental groups were statistically compared as "a" DC and N + SGF versus NC, "b" D + SGF and D + Glib verses DC. *$p < 0.001$, NS: non-significant.

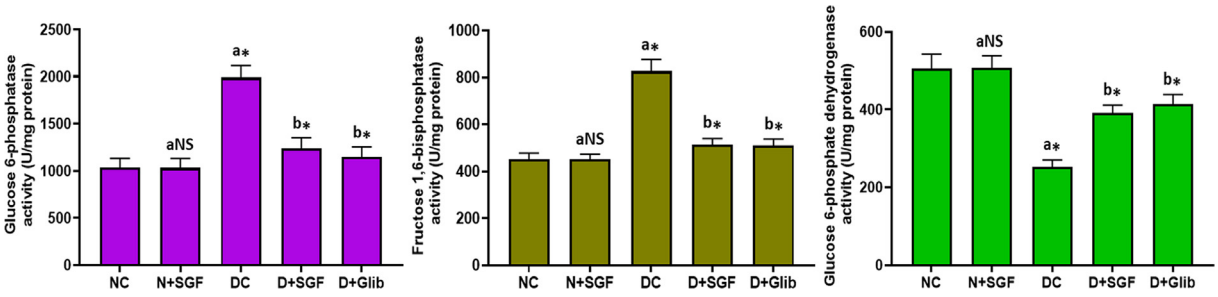

Fig. 3. Change of Glucose-6-phosphatase (G6Pase), Fructose-1,6-bisphosphatase (F1,6BP) and Glucose-6-phosphate dehydrogenase (G6PDH) activities in the liver of control and experimental rats. The units of enzymes activity were expressed as G6Pase - μM of phosphate released/h/mg protein, F1,6BP - μM of phosphate released/h/mg protein and G6PDH - μM of NADPH produced/min/mg protein. The results were expressed as mean ± SD (n = 6). The experimental groups were statistically compared as "a" DC and N + SGF versus NC, "b" D + SGF and D + Glib verses DC. *$p < 0.001$, NS: non-significant.

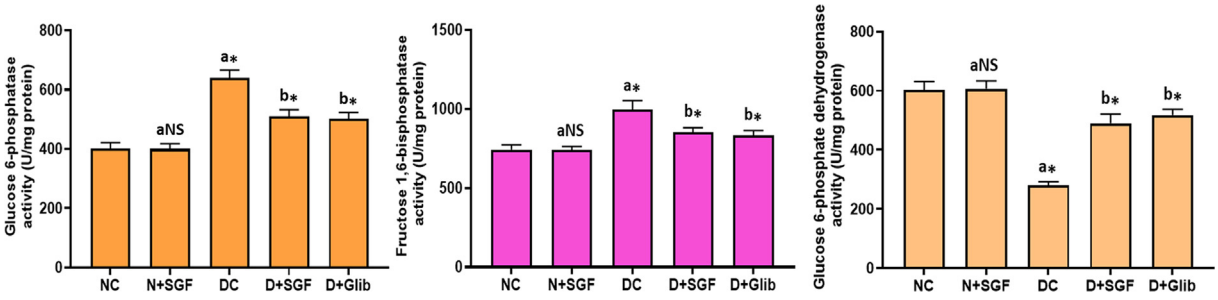

Fig. 4. Change of Glucose-6-phosphatase (G6Pase), Fructose-1,6-bisphosphatase (F1,6BP) and Glucose-6-phosphate dehydrogenase (G6PDH) activities in the kidney of control and experimental rats. The units of enzymes activity were expressed as G6Pase - μM of phosphate released/h/mg protein, F1,6BP - μM of phosphate released/h/mg protein and G6PDH - μM of NADPH produced/min/mg protein. The results were expressed as mean ± SD (n = 6). The experimental groups were statistically compared as "a" DC and N + SGF versus NC, "b" D + SGF and D + Glib verses DC. *$p < 0.001$, NS: non-significant.

trol rats did not depict any marked alterations in G6Pase, F1,6BP and G6PDH activities.

3.7. Effect of SGF on the level of glycogen and activities of GS and GP

Changes in the amount of glycogen, activity of glycogen synthase as well as glycogen phosphorylase were determined in the liver of experimental and control group rats and expressed in Fig. 5. The amount of glycogen and activity of glycogen synthase were markedly ($P < 0.001$) diminished whereas glycogen phosphorylase activity was markedly ($P < 0.001$) increased in the liver of diabetic rats. SGF and Glib treatment restored these changes to near normal. When SGF treated with normal control rats did not express any significant changes in the activities of glycogen phosphorylase, glycogen synthase and in the amount of glycogen.

4. Discussion

This study was explored the anti-hyperglycemic potency of SGF by assessing several parameters such as plasma glucose, insulin, C-peptide, Hb, HbA_{1C} and activities of some important enzymes which are playing major role in carbohydrate metabolism in the liver and kidney of STZ-induced diabetic rats. STZ is a pancreotoxic chemical that damage the β-cells of the islets of Langerhans which causes a significant diminution in insulin secretion resulting in hyperglycemia. In this study, significant elevation of plasma glucose and a marked reduction of C-peptide and insulin were observed in the STZ-induced diabetic rats. This results are comparable with earlier studies (Karthikesan et al., 2010; Hamza et al., 2021). Insulin was synthesized and secreted with C-peptide by pancreatic β-cells and enter in to the circulation. Due to STZ-induced damage of pancreatic β-cells, the level of C-peptide and insulin secretion were decreased, thereby plasma glucose level was increased. After administration of SGF, the diabetic rats expressed a marked elevation in C-peptide and insulin concentration and a marked decline in plasma glucose concentration. The decreased plasma glucose might be attributed to enriched use of glucose by the tissues through increased secretion of insulin from existing pancreatic β-cells stimulated by SGF in diabetic rats. The result confirms that SGF might be regenerating the pancreatic β-cells by its active compounds. Earlier studies reported that bioactive compounds like flavonoids, terpenoids, triterpenes, anthocyanin, saponins, phenolics, tannins, etc., increases insulin synthesis, decreases glucose level and precludes the progress of diabetic complications in STZ-induced diabetic rats (Lodhi and Kori, 2021; Germoush et al., 2020;Harley et al., 2020;Jiang et al., 2020a, 2020b; Barakat et al., 2020; Eluehike and Onoagbe, 2018). SGF also contains these bioactive compounds (Loganayaki et al., 2012; Andarwulan et al., 2012; Dethe et al., 2014) which might be the causative factor for the reduction in the concentration of glucose and increased concentration of C-peptide and insulin in STZ-induced diabetic rats.

In some diabetic cases, insulin will be normal but most of the tissues would be unable to utilize glucose, this is called glucose intolerance which causes hyperglycemia. To assess glucose intolerance, OGTT is one of the very common method that investigate the impairment of blood glucose regulation or glucose homeostasis. In this study, blood glucose level was markedly elevated after ingestion of glucose during OGTT in diabetic rats. In SGF administered diabetic rats, the concentration of blood glucose was raised to a peak and came back to fasting blood glucose ranges after 120 min. In contrast, the blood glucose concentration persisted at high concentration even after 120 min in untreated diabetic rats. This results illustrated that SGF might be ameliorating the impairment of glucose tolerance by reducing glucose absorption from the intestine and enhancing insulin secretion from the pancreas and stimulating insulin action on various tissues for glucose uptake by its active compounds (Lodhi and Kori, 2021; Germoush et al., 2020; Harley et al., 2020; Jiang et al., 2020a, 2020b; Barakat et al., 2020; Eluehike and Onoagbe, 2018).

Loss of body weight, wasting of muscle, loss of excessive hair, scaling, cataract, increased consumption of food and water, polyuria, dehydration, etc., are the characteristics of diabetic rats. In this study, body weight was markedly diminished in STZ-induced diabetic rats. This might be attributed to more utilization of fat and protein for energy production because diabetic rat cells may be unable to utilize glucose for energy production due to diminished action or secretion of insulin. Besides, increased protein catabolism to bestow amino acids for gluconeogenesis result in muscle waste and diminution of body weight (Srinivasan et al., 2014). This study also measured food and water consumption every day in control and experimental rats. The food and water consumption was markedly raised in diabetic rats; which might be attributed to decreased utilization of glucose by the tissues, thereby large amount of glucose excretion through urine that creates a continuous stimulation to consume excess food and water. The loss of body weight, high consumption of food and water prevented in SGF treated diabetic rats. This might be due to the improvement of glycemic control by the active compounds present in SGF (Lodhi and Kori, 2021; Germoush et al., 2020; Harley et al., 2020; Jiang et al., 2020a, 2020b; Barakat et al., 2020; Eluehike and Onoagbe, 2018).

During diabetic treatment, to assess the long-term glycemic control HbA_{1C} is one of the more appropriate marker. HbA_{1C} was increased in diabetic patients due to glycosylation of hemoglobin and its concentration was increased as directly proportional to the amount of fasting blood glucose. In diabetic condition, the high concentration of blood glucose reacts with Hb in non-enzymatic manner. Therefore, the concentration of total Hb was decreased

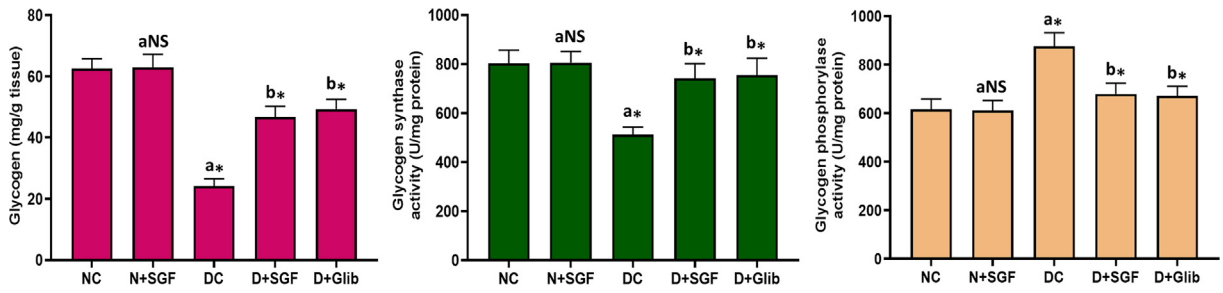

Fig. 5. Change of Glycogen level, Glycogen synthase (GS) and Glycogen phosphorylase (GP) activities in the liver of control and experimental rats. The units of enzymes activity were expressed as GS - μM of UDP generated/h/mg protein and GP - μM of phosphate released/h/mg protein. The results were expressed as mean ± SD (n = 6). The experimental groups were statistically compared as "a" DC and N + SGF versus NC, "b" D + SGF and D + Glib verses DC. *$p < 0.001$, NS: non-significant.

while HbA_{1C} was increased (Sundaram et al., 2012). This study also observed a significant decline in Hb and elevation in HbA_{1C} concentration in diabetic rats. SGF treatment diminished the concentration of HbA_{1C} thereby increased the Hb concentration in diabetic rats. Through this results, SGF has proved its anti-hyperglycemic effect by ameliorating glycemic control.

Endogenous glucose is mainly produced by liver and some amount from kidney through gluconeogenesis or glycogenolysis (Roden and Bernroider, 2003; Cersosimo et al., 1997). Endogenous glucose synthesis was raised in diabetic patients due to decreased pancreatic function and diminished uptake of glucose by the tissues result in hyperglycemia (Wajngot et al., 2001). Glucose uptake and utilization by the cells of various organ tissues were regulated by insulin through modulating several metabolic enzymes. Earlier studies reported that bioactive compounds like flavonoids, terpenoids, triterpenes, anthocyanin, saponins, phenolics, tannins, etc. enhance muscular uptake of glucose through insulin and non-insulin dependent pathways (Lodhi and Kori, 2021; Germoush et al., 2020; Harley et al., 2020; Jiang et al., 2020a, 2020b; Barakat et al., 2020; Eluehike and Onoagbe, 2018).

Glycolysis pathway is the hub of cellular metabolism which begins with the phosphorylation of glucose to glucose 6-phosphate by hexokinase (HK). HK is an isoenzyme playing major role in energy metabolism. In mammalian cells, hexokinases (HKs) are recognized as four isoforms which are involved in glucose oxidation (Wilson, 1995). Among these HKs, HK I-III have more affinity with glucose and these will be regulated through feedback inhibition by glucose 6-phosphate concentration of the cell. HK-IV or glucokinase has less affinity with glucose but mostly phosphorylates glucose and the enzyme activity is regulated by insulin, glucagon and glucokinase regulatory protein (Collier and Scott, 2004). In the liver HK-I and HK-IV are expressed more as compared with other HKs. According to earlier reports, liver HK plays major role on utilization of glucose and synthesis of glycogen (Postic et al., 2001) and its activity was reduced in diabetes and restored by insulin administration (Ferre et al., 1996). In this study, a marked decline in HK activity was found in the liver and kidney of diabetic rats. This might be attributed to diminished level of insulin; the observation is reliable with previous studies (Palsamy and Subramanian, 2009; Prasath and Subramanian, 2011; Sundaram et al., 2012; Srinivasan et al., 2014). After treatment with SGF, the HK activity was markedly elevated in the liver and kidney of diabetic rats. This elevation might be attributed to SGF mediated activation of insulin secretion from the remnants of pancreatic β-cells. SGF enhanced glucose metabolism and ameliorated glucose homeostasis by increasing HK activity of liver and kidney.

Pyruvate kinase (PK) is used to form pyruvate from phosphoenolpyruvate and yields an ATP molecule. PK consists of four isoforms, those are referred as L (liver-type), R (red blood cell-type), M1 and M2 (muscle-type) respectively. The PK-L is expressed in the liver at maximum levels and minimum amount is expressed in the kidneys, pancreatic β-cells and small intestine (Yamada and Noguchi, 1999), while PK-R is found only in the red blood cells. PK-M1 is found in the brain, heart and skeletal muscle, whereas PK-M2 is found in other tissues (Noguchi et al., 1991). Earlier study found a marked reduction in PK-L activity and it is restored by insulin treatment in diabetic rats (Yamada and Noguchi, 1999). During diabetes, the decreased PK activity might be the reason for reduction in the glucose metabolism and synthesis of ATP. The present study observed a marked decline in PK activity in the liver and kidney of STZ-induced diabetic rats resulted in a lowered glycolysis and activated gluconeogenesis. Similar results were demonstrated by earlier studies (Palsamy and Subramanian, 2009; Prasath and Subramanian, 2011; Srinivasan et al., 2014). The PK activity were reverted to near normal in the liver and kidney of SGF treated diabetic rats, this might be attributed to the bioactive compounds present in the SGF (Loganayaki et al., 2012; Andarwulan et al., 2012; Dethe et al., 2014).

Glucose-6-phosphatase (G6Pase) plays a major part in the glucose homeostasis. It is mostly found in the liver and kidney, it helps to synthesis glucose during starvation or prolonged fasting and diabetes mellitus (Bouché et al., 2004). In glycogenolysis and gluconeogenesis pathways, G6Pase is involved in the process of dephosphorylation, in this phase glucose-6-phosphate is converted in to free glucose. This reaction takes place in the endoplasmic reticulum and this enzyme is associated with glucose-6-phosphate transporter, it hydrolyzes the glucose-6-phosphate to glucose and phosphate (Chou et al., 2002). G6Pase is activated by cAMP and inhibited by insulin. In agreement with earlier studies (Palsamy and Subramanian, 2009; Prasath and Subramanian, 2011; Srinivasan et al., 2014), the current study also found significant amelioration in G6Pase activity in the liver and kidney of STZ-induced diabetic rats. This might be attributed to diminution of insulin. Earlier reports illustrated that increased G6Pase activity affects glucose utilization by liver and activates glucose synthesis (Trinh et al., 1998). In SGF administered diabetic rats, G6Pase activity was reverted to near normal, this might be attributed to the bioactive compounds which are found in the SGF (Loganayaki et al., 2012; Andarwulan et al., 2012; Dethe et al., 2014).

In gluconeogenic pathway, Fructose-1,6-bisphosphatase (F1,6BP) acts as a rate-limiting enzyme and involved in the step of dephosphorylation of fructose-1,6-bisphosphate converted in to fructose-6-phosphate (Pilkis and Claus, 1991). It is mostly found in liver and kidney but slightly expressed in the β-cells of pancreas. This study observed a marked elevation in the activity of F1,6BP in the liver and kidney of STZ-induced diabetic rats. This result is concomitant with previous reports (Palsamy and Subramanian, 2009; Prasath and Subramanian, 2011; Srinivasan et al., 2014). During diabetes, the increased activity of F1,6BP might be a conceivable way for the activation of endogenous glucose synthesis from glycerol *via* gluconeogenesis (Nurjhan et al., 1992). SGF treatment was significantly reduced the activity of F1,6BP in the liver and kidney of diabetic rats by inhibiting the gluconeogenesis through gluconeogenic substrates whereas preventing direct actions on glycolysis, glycogenolysis, and citric acid cycle and thereby restores the glucose homeostasis.

During anaerobic glycolysis, LDH converts pyruvate into lactate to generate energy, this being the last step of glycolysis pathway, occurs in the cytosol as well as in the mitochondria (Kavanagh et al., 2004; Bouché et al., 2004). LDH is composed of two subunits, those are named as H (heart-type) and M (muscle-type); synthesis of these subunits are regulated by two different genes. The activity of LDH is found to be regulated by glucose, insulin, NADH at the same time increases its activity by cytosolic ATP, $Ca^{2+}$and mitochondrial membrane potential (Ainscow et al., 1999). In tissues, diminished LDH activity could be vital to confirm that a high ratio of both NADH and pyruvate, provided by glycolysis, is consequently oxidized by mitochondria. In this study, the activity of LDH was markedly increased in the liver and kidney of STZ-induced diabetic rats. Similar results were shown by previous studies (Palsamy and Subramanian, 2009; Prasath and Subramanian, 2011). During diabetes, the elevated LDH activity might disturb the normal metabolism of glucose and interfere with insulin secretion by pancreatic β-cells. The activity of LDH was reverted to near normal in the liver and kidney of diabetic rats treated with SGF by modulating the ratio of NADH and pyruvate thereby ameliorating the process of oxidation of glucose (pyruvate) in the mitochondria.

G6PDH is a regulating enzyme of pentose phosphate pathway which produces NADPH, needed for restoration of reduced glutathione from oxidized glutathione. Earlier studies reported that

NADPH generated by G6PDH is mandatory for reactive oxygen species (ROS) production like superoxide radicals and nitric oxide radicals and eradication of these radicals through catalase and glutathione peroxidase (GPx) in the hepatic and extrahepatic tissues (Park et al., 2006). Increased glutathione levels were associated with increased G6PDH activity and reduced oxidative stress. A significant reduction in the activity of G6PDH was observed in the liver and kidney of diabetic rates of this study. This result is comparable with previous studies (Palsamy and Subramanian, 2009; Prasath and Subramanian, 2011; Srinivasan et al., 2014). The diminished activity of G6PDH might also be a key player in the progress of diabetic complications. In SGF treated diabetic rats, the G6PDH activity was significantly raised to near normal, this might be attributed to the bioactive compounds which are found in the SGF (Loganayaki et al., 2012; Andarwulan et al., 2012; Dethe et al., 2014).

Glycogen is a stored form of glucose, synthesized by glycogen synthase and stored in the tissues depending upon the insulin secretion and action because insulin plays crucial role in glycogen storage by activating glycogen synthase and suppressing glycogen phosphorylase (Pederson et al., 2005). In the tissues, non-oxidative glucose is removed by glycogen synthase, it is a regulating enzyme, it transfers glucose from UDP-glucose to glycogen. Glycogen synthase is composed of two isoforms, one is found only in the liver similarly the second isoform is expressed in adipose tissue, cardiac and skeletal muscle, brain and kidney. The glycogen synthase activity is modulated by hormone signaling and low glycogen content of cells (Parker et al., 2004). Glycogen phosphorylase, separate glucose molecules by cleaving α $(1 \rightarrow 4)$ linkage of glycogen. In glycogenolysis pathway, it acts as a rate-limiting enzyme. The activity of glycogen phosphorylase is controlled by glucose, glucose-6-phosphate, AMP and ATP through allosteric binding (Bollen et al., 1998). This study found a marked reduction of glycogen and glycogen synthase activity and significant elevation of glycogen phosphorylase activity in the liver of STZ-induced diabetic rats. Similar results were demonstrated by previous studies (Palsamy and Subramanian, 2009; Prasath and Subramanian, 2011; Srinivasan et al., 2014). The alteration of glycogen content, glycogen phosphorylase and glycogen synthase might be attributed to decreased level of insulin because it is very essential for glycogen synthesis and storage in the tissues. SGF treatment were restored the content of glycogen, activities of glycogen phosphorylase and glycogen synthase by activating the secretion of insulin from pancreatic β-cell remnants in diabetic rats.

5. Conclusion

In this study, the efficacy of SGF extract in the mitigation of diabetes mellitus is explored by assessing the restoration of enzymes which are essential for the metabolism of carbohydrate in STZ-induced diabetic rats. The results of this study revealed that SGF stimulated the activities of glycolytic enzymes and regulated the metabolism of glucose in the liver and kidney of diabetic rats by enhancing insulin secretion from the existing pancreatic β-cells. This might be attributed to bioactive compounds present in the SGF. Further research is warranted to explore the precise molecular mechanism of SGF extract for its antidiabetic actions and to isolate the bioactive compounds which are accountable for antidiabetic effect.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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