Research Article

Study of steroid induced hyperglycemia against traditional hypoglycemic plant extracts in rat model

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Abstract

Background and Objective: Now a days corticosteroid drugs are used as a treatment and longtime use of the drug elevates the blood glucose level results in steroid hyperglycemia. Moreover, treatment of study was undertaken to examine the effect of *Gynura procumbens* plant on steroid induced hyperglycemia in rats. Therefore, present of hyperglycemia by synthetic drug may develop health risk along with adverse effects. **Material and methods:** Fifteen Long evan male rats were assigned into three different groups and each group had 5 rats for 21 days. . Group T_0served as negative control, Group T_1 served as positive control was treated with dexamethasone intramuscularly with 5 mg/kg body wt. Group T_2served as treatment group injected with dexamethasone with 5 mg/kg body wt. intramuscularly and treated with *Gynura procumbens* ethanolic extract with 150 mg/kg body wt. orally for 21 consecutive days. After that extract effect was observed on blood glucose, lipid profile, HbA1c and insulin level by biochemistry analyzer and live body weights were weighed and recorded by digital balance. Histopathology of rat pancreases was also observed for all of groups. **Results and conclusion:** Blood glucose level was significantly increased than the negative control group. The HbA1c and lipid profile values were greatly enhanced while the final body weight of different groups met a significant reduction from the initial body weight. Insulin level showed negligible changes which was statistically significant. Histopathological changes indicate to neoplastic growth over the Langerhans cells. At the end this study shows that chronic steroid therapy induces hyperglycemia that is irresponsive to *Gynura procumbens* treatment.

***Keywords*:** *Gynura procumbens,* dexamethasone, hyperglycemia, langerhans cells, steroid

Introduction

Hyperglycemia refers to high levels of glucose in the blood, is a fast growing health problem throughout the world. It occurs when the body does not produce or use enough insulin. Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by persistent hyperglycemia (Neelesh et al., 2010). Hyperglycemia accompanied by symptoms of polyuria, polydipsia, polyphagia and weight loss. These abnormalities are due to insulin deficiency of β-cells and/or subsensitivity to insulin in peripheral cells (Rajasekaran et al., 2005), primarily changing carbohydrate metabolism and secondarily of lipids and proteins (Al-Attar and Zari, 2010). Recent data from the International Diabetes Federation (IDF) indicates that Diabetes mellitus affects over 366 million people worldwide might increase to 552 million or even more by the year 2030 (Whiting et al., 2011). Over 50 years glucocorticoid use leads to steroid-induced diabetes mellitus complication (Hwang and Weiss, 2014). People who need to take steroids for longer periods of time are the most susceptible to develop steroid induced hyperglycemia.

Corticosteroid is widely used as medicine and frequently prescribed as anti-inflammatory, immunosuppressant and replacement therapy (Van-Raalte et al., 2013). The development of this form of diabetes during steroid therapy

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in human beings is well known (Bookman et al., 1953). Steroid elevates blood glucose level by increasing gluconeogenesis and inhibiting glucose uptake into muscles. It has a complex effect on beta cell function (Chen et al., 2017). Glucocorticoids reciprocally up regulates and down regulates Phosphoenyl pyruvate carboxykinase (PEPCK) in liver and adipose respectively (Cadoudal et al., 2005). This results in a build up of free fatty acids in the blood, which result in insulin resistance and increase gluconeogenesis.

The available glucose-lowering drugs have side effects and are expensive for the large diabetic population of developing countries. Thus, WHO expert committee on diabetes recommended that traditional medicinal herbs can be used for the treatment of diabetes. Recently *Gynura procumbens* plant commonly used as hypoglycemic agent. The bioactive compounds of *Gynura procumbens* is flavonoids and glycosides (Akowuah et al., 2001, 2002). Kaempferol may be a naturally occurring flavonol, a type of flavonoid, it is slightly soluble in water and highly soluble in hot ethanol. Most importantly, small molecule kaempferol (3,4′,5,7-tetrahydroxyflavone) anti-diabetic agent that improves peripheral insulin sensitivity and protects against pancreatic β-cell dysfunction (Alkhalidy et al., 2015).

Reviewing the previous research work, there is little knowledge about this plant to treat corticosteroid induced hyperglycemia on rat. Therefore, present study will be undertaken to evaluate the possible antihyperglycemic activity of the ethanolic extract of *G. procumbens* during corticosteroid therapy on hyperglycemic rats. So, the general objectives of this study is to determine the antihyperglycemic effect of *G. procumbens* leaves extracts with the determination of blood glucose level, plasma insulin concentration, lipid profile and HbA1C level on corticosteroid induced hyperglycemic rat treated with extract. The body weight on corticosteroid induced hyperglycemic rats treated with *Gynura procumbens* leaf extract were determine and also observe the histopathological changes of pancreas in steroid induced hyperglycemic rat.

Materials and methods

This research work was conducted from 13 October 2020 to 19 November 2020 at animal laboratory under the department of Physiology and Pharmacology in Hajee Mohammad Danesh Science and Technology University, Dinajpur to evaluate the hypoglycemic effect of *Gynura procumbens* ethanolic extract on corticosteroid induced hyperglycemic rats.

Management of experimental rats

The weight 50 to75gm of Long evans (out bred) male rats of 35 days old were obtained from Animal Resource Facility, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). Animals were acclimatized in the laboratory for 15 days before initiating the experimental works. The rats were housed in wire cages measuring 30×13×15 cm at room temperature (28±5)°C under a light/dark cycle of 12 hours. Standard commercial rat pellet diet was supplied by ICDDR,B with water ad-libitum throughout the experimental period.

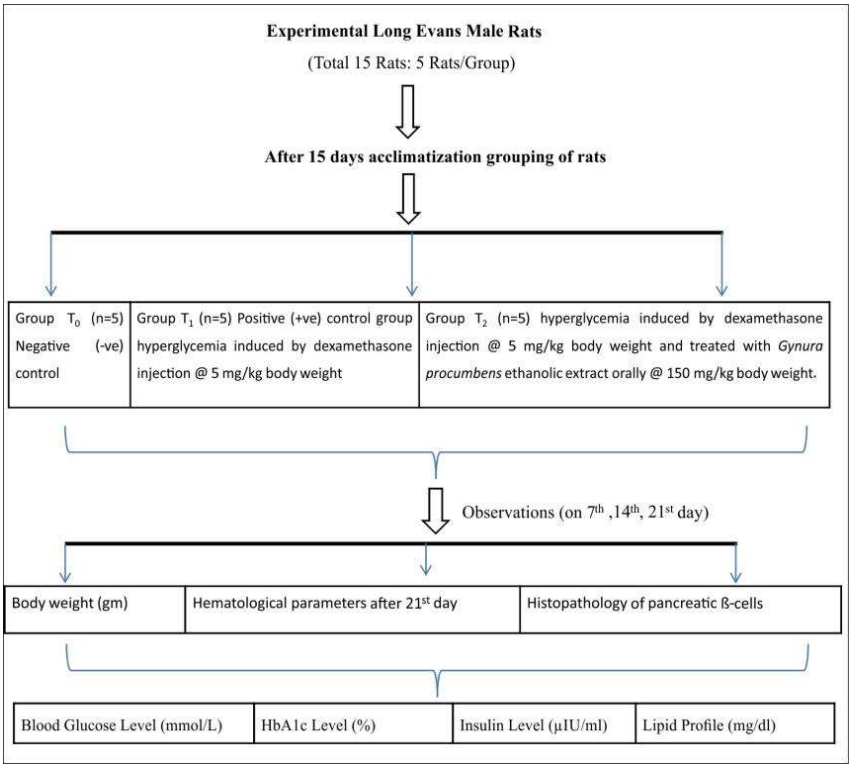

Figure 1. Experimental protocol

Figure 2. *Gynura procumbens* Plant

Collection of drug and equipments

Dexamethasone sodium (Dextason) injection was collected from Ziska pharmaceuticals Ltd. 1ml syringe were used for intamuscular injection. Sugar check machine and sugar monitoring test strips were collected.

Induction and determination of hyperglycemia in rats

Corticosteroid induced hyperglycemia was introduced by injecting dexamethasone injection (Dextason, each ampule contains 5mg in 1 ml) intamuscularly @5mg/kg body weight. After 3 days of injection the fasting blood sugar was determined on strip method by Sugar Check machine. Blood was obtained from tail vein of overnight fasting rats and blood glucose levels 12.8 mmol/L were considered as hyperglycemia. The reference values of normal glucose is about 4.5 to 6.1 mmol/L (Tietz, 1995). Fasting blood glucose was measured on day 1(before the experiment starts) and then 4^{th}, 7^{th}, 14^{th}, 21^{st} day for continuous monitoring.

Collection preparation and administration of extract

Leaves of *G. procumbens* were collected from the faculty of Agriculture, HSTU and then it was cultivated under proper conditions.

Firstly the *Gynura procumbens* leaves were collected. Fresh leaves were washed, weighed and dried in oven (Sheldon Manufacturing, Inc., USA) at 45°C for 3 days. After drying, dried leaves were blended into powder form. Ethanolic extract of *G. procumbens* leaves were prepared according to the method of Zhang and Tan (2000). Fresh leaves of *G. procumbens* (30 gm) were washed, blended and mixed with 95% ethanol (200 ml) for 7 days at room temperature. The extract was then filtered, obtained supernatant was concentrated by using rotary evaporator at 40°C. To yield yellowish dark green powder of *G. procumbens* crude ethanolic extract was stored at normal freezing temperature (4°C).

The prepared extracts were fed orally @150 mg/kg body weight to the treatment group with the help of a dropper. Mortality and general behaviors of the animals were closely obseved for the first 4 hours and intermittently for the next 6 hours.

Recording of different parameters

Body weight was taken on 1^{st}, 7^{th}, 14^{th}, 21^{st} day with the help of an electric balance.

For estimation of blood glucose level blood samples were collected from tail vein at 1^{st}, 7^{th}, 14^{th}, 21^{st} day. A drop of blood was poured on the test zone of the strip and Sugar check machines active monitor quickly find the glucose level and expressed it in mmol/L.

At the end of the experiment blood samples were collected by heart puncture to determine plasma insulin concentration. Blood samples were centrifuged for 10 minutes at 3000 rpm by the centrifuge machine and the serum samples were seperated into microtubes, stored at -20°C and analyzed by auto analyzer. The amount of 1 ml of blood was collected into Vacuette EDTA tubes for determination of HbA1c(%) and lipid profile(mg/dl). Estimations were carried out by Hemocue machine and Dimension EXL 200 respectively.

Histopathology was performed to find the rat pancreatic cells of all groups and observed under microscope at 10x objective.

Results

The body weight of different groups were almost similiar at the initial day (Table 1 and Figure 3). But the body weights were varied significantly with the advancement of ages. Here body weight of positive control group T_1(156.0±0.13) was significantly decreased from the negative control T_0 (204.6±0.13) at the last 21^{st} day and after treatment it showed a slight weight gain at T_2 (163.0±0.13).

Table 1. Effect of *Gynura procumbens* plant extracts on live body weight (gm) in steroid induced hyperglycemic rats (n=5)

Groups	Day 0 (Mean ± SE)	Day 7 (Mean ± SE)	Day 14 (Mean ± SE)	Day 21 (Mean ± SE)
T_0	$222.4^{a} \pm 0.19$	$226.2^{a} \pm 0.13$	$210.5^{a} \pm 0.14$	$204.6^{a} \pm 0.13$
T_1	$224.0^{a} \pm 0.19$	$175.4^{c} \pm 0.13$	$164.0^{c} \pm 0.14$	$156.0^{c} \pm 0.13$
T_2	$219.2^{a} \pm 0.19$	$176.5^{b} \pm 0.13$	$171.3^{b} \pm 0.14$	$163.0^{b} \pm 0.13$
P value	0.110**	0.049**	0.056**	0.048**

Values with the different superscripts in the same column are statistically significant at $p<0.01$; N.B: T_0= Negative Control, T_1= Positive Control and T_2= Treatment with ethanolic extract of insulin plant @150 mg/kg body weight (2.5 ml/kg). Here ** denotes 1% level of significance. Figures indicate the Mean ± SE (standard Error).

The blood glucose levels were significantly decreased in the negative control T_0 (4.15±0.07) group on 21st day (Table 2 and Figure 3). Whereas the remaining two groups met an increased blood glucose level T_1(7.14±0.07) and T_2 (8.35±0.07).

The cholesterol level at peak on T_2 group (140.5 mg/dl). HDL level was peak at T_0 (53.23±0.14) group but the level significantly declined at T_1 (50.23 ± 0.14) and T_2 (13.60 ± 0.14) group respectively (Table 3 and Figure 3). In case of LDL T_2 showed highest value than the normal animal group T_0 (10.37± 0.14). And in case of positive control group T_1 (13.38 ± 0.14) indicates a higher LDL level than negative control group. Triglyceride was at peak level on T_2 (292.3± 0.15) group. In case of negative and positive control group triglyceride level was T_0 (167.2 ± 0.15) & T_1 (147.2± 0.15).

The HbA1C levels of different groups show a significant difference (Table 4 and Figure 3). Treatment group T_2 denotes the highest value 2.87± 0.02 and group T_1 represents (2.27± 0.02) which is higher than normal group. While in case of insulin level T_1 represents the highest value (0.408± 0.01) and T_0, T_2 shows (0.344± 0.01), (0.356 ± 0.01) respectively with negligible changes.

Gross and Microscopic changes

Gross changes were observed after postmortem and normal animal groups showed a regular structure of the visceral organs. While in case of steroid induced hyperglycemia fluid accumulation on the intestine were observed and the treatment group met detrimental effects like enteritis and acute pancreatitis.

After histopathology pancreas of normal rat represents Langerhans cells in the middle with the secreting glands in the periphery (Figure 4).

Table 2. Effect of *Gynura procumbens* plant extracts on blood glucose level (mmol/L, mean±SE) in steroid induced hyperglycemic rats (n=5)

Groups	Day 0 (Mean ± SE)	Day 7 (Mean ± SE)	Day 14 (Mean ± SE)	Day 21 (Mean ± SE)
T_0	$5.76^{a} \pm 0.06$	$6.08^{c} \pm 0.07$	$5.67^{c} \pm 0.04$	$4.15^{c} \pm 0.07$
T_1	$5.43^{a} \pm 0.06$	$9.90^{a} \pm 0.07$	$10.49^{a} \pm 0.04$	$7.14^{b} \pm 0.07$
T_2	$5.26^{a} \pm 0.06$	$8.70^{b} \pm 0.07$	$7.02^{b} \pm 0.04$	$8.35^{a} \pm 0.07$
P Value	0.010**	0.016**	0.005**	0.014**

Values with the different superscripts in the same column are statistically significant at p<0.01; N.B: T_0= Negative Control, T_1= Positive Control and T_2= Treatment with ethanolic extract of insulin plant @150 mg/kg body weight (2.5 ml/kg). Here ** denotes 1% level of significance. Figures indicate the Mean ± SE (standard Error).

Table 3. Effect of *Gynura procumbens* plant extracts on lipid profile (mg/dl) in steroid induced hyperglycemic rats (n=5)

Groups	Cholesterol (Mean ± SE)	HDL (Mean ± SE)	LDL (Mean ± SE)	Triglyceride (Mean ± SE)
T_0	$54.42^{c} \pm 0.20$	$53.23^{a} \pm 0.14$	$10.37^{c} \pm 0.14$	$167.2^{b} \pm 0.15$
T_1	$120.5^{b} \pm 0.20$	$50.23^{b} \pm 0.14$	$13.38^{b} \pm 0.14$	$147.2^{c} \pm 0.15$
T_2	$140.5^{a} \pm 0.20$	$13.60^{c} \pm 0.14$	$18.42^{a} \pm 0.14$	$292.3^{a} \pm 0.15$
P Value	0.118**	0.062**	0.060**	0.066**

Values with the different superscripts in the same column are statistically significant at p<0.01; N.B: T_0= Negative Control, T_1= Positive Control and T_2= Treatment with ethanolic extract of insulin plant @150 mg/kg body weight (2.5 ml/kg). Here **denotes 1% level of significance. Figures indicate the Mean ± SE (standard Error).

Table 4. Effect of *Gynura procumbens* plant extracts on HbA1C level (%) and Insulin level (ng/ml) in steroid induced hyperglycemic rats (n=5)

Parameters	Groups			P Value
	T_0 (Mean ± SE)	T_1 (Mean ± SE)	T_2 (Mean ± SE)	
HbA1C (%)	$1.56^{c} \pm 0.02$	$2.27^{b} \pm 0.02$	$2.87^{a} \pm 0.02$	0.002**
Insulin (ng/ml)	$0.344^{b} \pm 0.01$	$0.408^{a} \pm 0.01$	$0.356^{ab} \pm 0.01$	0.001**

Values with the different superscripts in the same column are statistically significant at p<0.01; N.B: T_0= Negative Control, T_1= Positive Control and T_2= Treatment with ethanolic extract of insulin plant @150 mg/kg body weight (2.5 ml/kg). Here **denotes 1% level of significance. Figures indicate the Mean ± SE (standard Error).

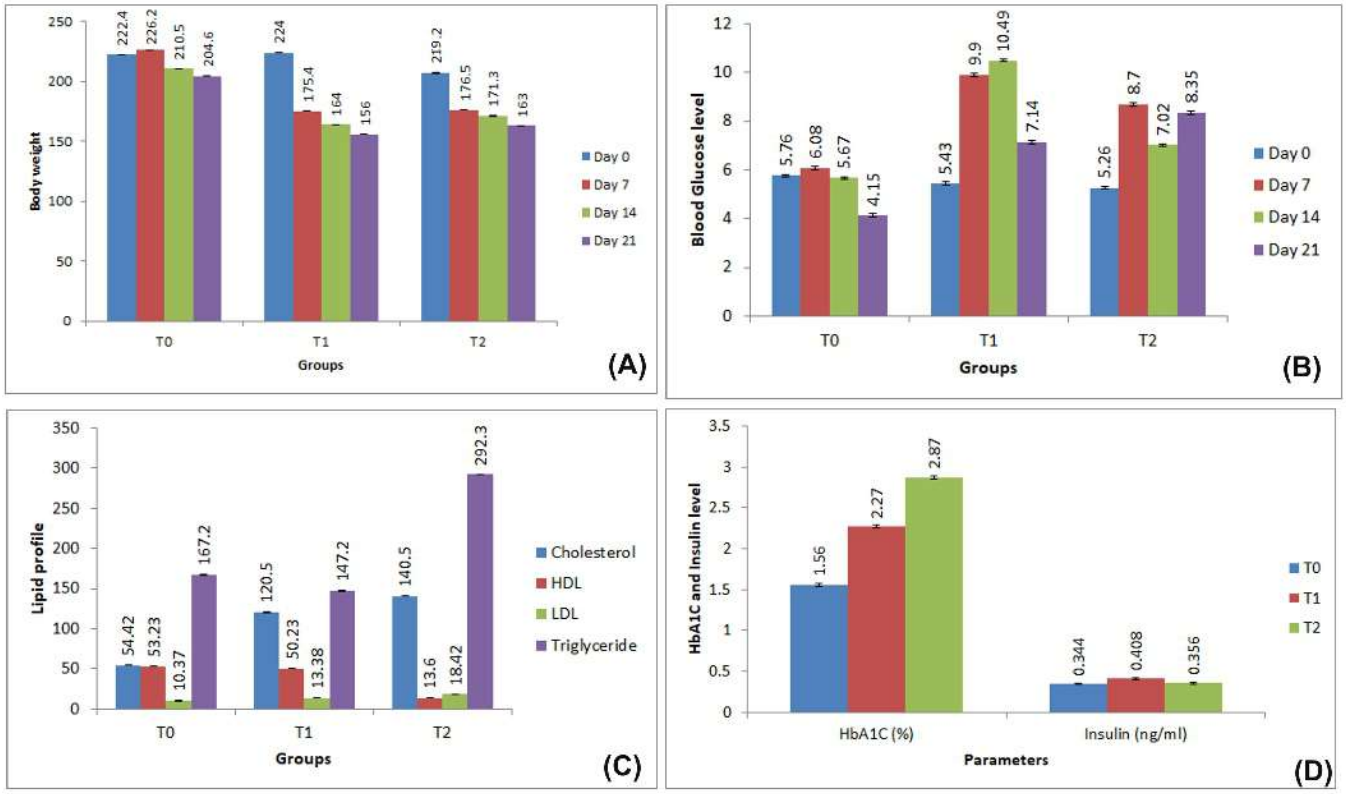

Figure 3. Effect of *Gynura procumbens* plant extracts on **(A)** live body weight, **(B)** blood glucose, **(C)** lipid profile, **(D)** HbA1C and Insulin level

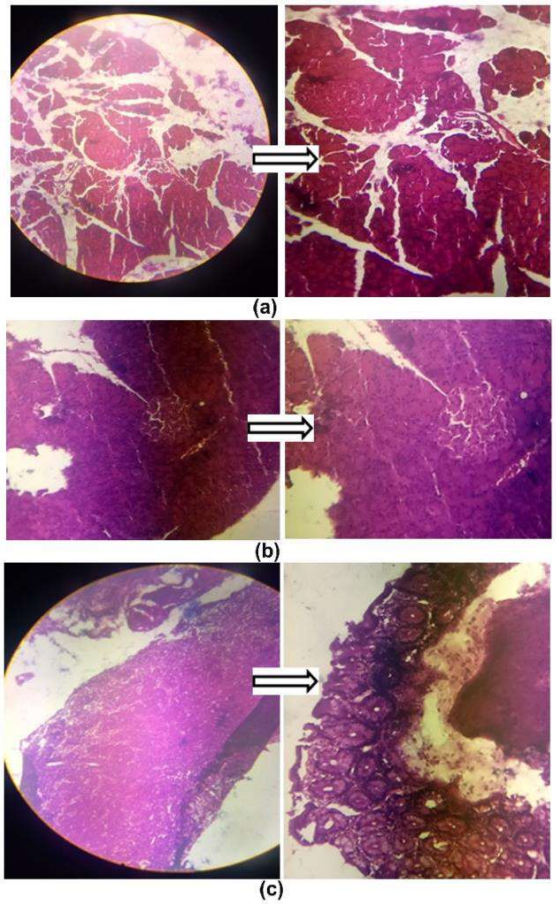

Figure 4. Histological observations for: (a) Normal rat pancreas, (b) Pancreas of hyperglycemic rat, (c) Rat pancreas of treatment group

Hyperglycemic pancreases showed fragmented Langerhans cells. One of the Langerhans cells was intact with alpha, beta and delta cells while another one was empty without any cells inside due to the prolonged effect of steroid medication.

Rat pancreases of treatment group showed a negative response on the pancreatic islets cells. Only the secretory cells were present without distinct islets of Langerhans. Neoplastic growth over the Langerhans cells was found due to the prolonged corticosteroid therapy.

Discussion

The experiment was conducted to determine the consequences of steroid induced hyperglycemia on body weight, blood glucose level, lipid profile, HbA1C and insulin levels against traditional hypoglycemic plant extract.

The final body weight of negative control and treatment group were significantly higher ($P<0.01$) than the positive control group and is similar with the findings of Khalid et al. (2013). Who showed significant recovery in body weight gain after 14 days of *G. procumbens* extract administration. Atangwho et al. (2012) described that body cells rarely access glucose, and body weight losses due to fats and tissue proteins are breakdown for energy supply in hyperglycemia. That is similar with the present study. Saad et al. (1993) described weight gain as distressing side effect of long term glucocorticoid therapy that might support the present study.

Blood glucose levels were normal in negative control group but the remaining two groups met an increased blood glucose level. Khalid et al. (2013) reported that the extracts of *G. procumbens* did not produce any significant effect on fasting blood glucose at an acute dose**,** even after 7 h. Which are similar to the present study. Hui-Wen et al. (2011) also described that diabetic rats treated with ethanolic extract of *G. procumbens* reduces fasting blood glucose in a dose independent manner due to the presence of antagonistic substances at higher doses of the ethanolic extract. But the present study fails to meet the anti-hyperglycemic effect. Zurina et al. (2010) reported that *G. procumbens* water extract and metformin had significantly decreased fasting blood glucose levels while present study shows an inverse result. Saad et al. (1993) described that about 4-8% dexamethasone can induce hyperglycemia in 100% of animals and glucocorticoids therapy increases visceral fat which results insulin resistance and hyperglycemia. In this study plant extracts become irresponsive to steroid hyperglycemia due to severe induction.

Cholesterol level increases in positive control and treated group. Likewise LDL and Triglyceride levels were significantly ($P<0.01$) increased in both hyperglycemic and treated groups. HDL was higher in normal animals and decreased statistically ($P<0.01$) in T_1 and T_2 groups. According to Poorsoltan et al. (2013) the triglyceride levels are higher than normal groups in both diabetes and severe diabetes groups. Bardini et al. (2012) reported lipid profile abnormalities in both diabetes and severe diabetes group those are similar to our study. Nazri et al. (2019) suggested that the *G. procumbens* extract reduced plasma concentrations of TG, TC, and LDL and increased plasma HDL. Which contradict the present study. A previous study by Corbi et al. (2018) reported that phenolic acids were able to reduce Cholesterol, LDL and increase HDL. Another study by Zhang and Tan (2000) also reported that serum Cholesterol and Triglyceride in hyperlipidaemic rats were reduced with *G. procumbens* supplementation. But the present study is dissimilar with reports data (Corbi et al., 2018; Zhang and Tan, 2000).

According to Al-Yassin and Ibrahim (1981) chronic hyperglycemia may leads to increased glycosylated hemoglobin (HbA1c) reacting between excess glucose in the blood and hemoglobin. The present study also reveals the same findings. Rajasekaran et al. (2005) described that Oral administration of *G. procumbens* aqueous and ethanolic extracts have shown significant reduction on the HbA1c level which was due to improved glucose metabolism as well as increased hemoglobin synthesis. Another findings from Palsamy and Subramanian, 2008 is *Gynura procumbens* extract reduces HbA1c level and the risk of diabetic complication pathogenesis. But this study disagree with Rajasekaran et al., (2005) and Palsamy and Subramanian (2008). In case of insulin level T_1 group represents the highest value. No significant changes on plasma insulin levels were found between the control and treated groups which is similar with the findings by Zurina et al. (2010) they mentioned *G. procumbens* water extract acts at the peripheral level and it did not stimulate insulin secretion and inhibited endogenous insulin production did not activate the β cells of pancreas. Hui-Wen et al. (2011) described that, oral administration of *G. procumbens* extracts did not stimulate insulin secretion. That is consistent with the present study.

In case of gross changes hyperglycemic rats showed slight fluid accumulation in the intestinal parts and treatment group represents necrosed gut with acute pancreatitis. Hadi et al. (2016) reported that the size and number of pancreatic islets were decreased in hyperglycemic rats in comparison with normal rats, which was in consistent with histopathological data obtained from the current study. El-Esawy et al. (2016) described that hyperglycemic rat pancreas demonstrated degeneration and vacuolizations in the islet of Langerhan's cells, decreasing in islets size, β-cell number and also in the architecture of the islets. Which support the present study findings.

Conclusion

In conclusion, it can be proven that *Gynura procumbens* extract has a little extend of antihyperglycemic activity in context of live weight, blood glucose and HbA1c in diabetic rat produced by steroid therapy. It is however depicted that *Gynura procumbens* extract has a negative impact on lipid profile as the value of LDL, triglyceride has been increased. In histopathology, no beneficial effect has been observed in necrosed gut as well as pancreases in steroid therapeutic diabetic rat compare to negative control rats. This steroid hyperglycemia is very dangerous and difficult to control. The *Gynura procumbens* plant extract did not respond against steroid hyperglycemia though it has anti-hyperglycemic properties. It might be due to severe level of steroid drug induction which hinders the natural plant extract to execute its action.

For further research it can be recommended that *Gynura procumbens* extract can be compared with the Synthetic insulin therapy in steroid induced rats.

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