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Effect of syringin (eleutheroside B) on the physiological and hematological parameters in STZ induced Type II diabetic Wistar rats

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Abstract: To investigate the physiological indices such as body weight, food and fluid drinking concern to antidiabetic properties of syringin and its useful outcome on hematological parameters in streptozotocin stimulated diabetic rats. Six normal and 18 diabetic rats totally 24 rats have been used for the present investigation. Streptozotocin was injected in male Wistar rats to induce diabetes through intraperitoneal route. After the confirmation of diabetes, the test animals were treated with distilled water through oral route or syringin 5 mg/kg body weight/ rat /day for 10 days. The diabetic treated groups compared with the controls were evaluated based on their hematological parameters such as red blood cells, white blood cells and its functional indices. The blood glucose levels significantly decreased in syringin injected rats. The intake of water and feed in diabetic rats were significantly decreased, whereas after syringin administration the weight loss was minimized. Congruently, the level of red blood cells, white blood cells and their functional key characters were also considerably enhanced. It can be conjectured that syringin has antihyperglycemic properties. In addition, it can positively amend some hematological parameters.

Keywords: Antihyperglycemic, diabetes, hematology, syringin, streptozotocin.

INTRODUCTION

Diabetes mellitus (DM) is a complex, chronic metabolic disorder of carbohydrates, proteins and fat due to complete or comparative scarcity of insulin secretion with/without fluctuating amount of insulin resistance. It is categorized with long-lasting high blood glucose that may probably lead to morbidity and death rate (Mohammed *et al.*, 2007). The number of individuals suffering from DM universal is rising at a frightening rate. It is predicted that about 366 million people are likely to be diabetic by the year 2030 (Wild *et al.*, 2004). This is since that none of the antidiabetic drugs might give an extensive period glycemic control exclusive of causing any unfavorable side effects (Singh *et al.*, 2007). In the meantime, therapeutic plants and their derived metabolites that are effective in controlling plasma glucose level with negligible side effects are generally used in under developed countries as substitute therapy (Tanko *et al.*, 2007).

Phytochemicals are identified to have varying antioxidant activities (Egea *et al.*, 2017; Huang *et al.*, 2009; Iranshahy *et al.*, 2017; Liu *et al.*, 2015; Tafesse *et al.*, 2017). A phenyl propanoid glycoside known as *syringin* belongs to eleutheroside derivative. Several plants such as *Edgeworthia chrysantha*, *Jasminum mesnyi*, *Musa paradisiaca*, *Acanthopanax senticosus*, etc. has been identified that, they contain bioactive compound called *syringin*. The pharmacological possessions of *syringin* includes scavenging the free readicals, protection against antidiabetic effect, anti-nociceptive action, neuronal cell damage, inhibition of apoptosis, anti-inflammatory potential, anti allergic effect, etc. (Kim *et al.*, 2005; Kim *et al.*, 1999; Kim *et al.*, 2010; Yang *et al.*, 2010). Recently, we have evaluated the antidiabetic, antioxidant and antiulcer nature of *Musa paradisiaca* and *syringin* in experimental mice (Ahmad *et al.*, 2015; Rao *et al.*, 2016; Rao *et al.*, 2015).

Still, there is minimum information on methodical writing to validate its folkloric practice. Hence, this research is to examine the consequence of syringin as an antidiabetic agent and beneficial amelioration of some hematological parameters in DM rats.

MATERIALS AND METHODS

Chemicals

Streptozotocin and the bioactive compound syringin were availed from Sigma-Aldrich, St. Louis, USA. Analytical graded reagents were used in the current study.

Experimental animals

Westar strain male albino rats (160±20g) were obtained from Universiti Sains Malaysia, Kelantan, Malaysia. In lined polypropylene cages with husk bed the animals were accommodated arbitrarily in spacious condition and kept under the controlled environment (temperature 22°C±3°C; 12:12±1h light/dark cycle; relative humidity 55%±10%). Previous to the experiments, all animals were acclimatized to normal husbandry circumstances for one

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week to overcome stress. Commercial pellet was fed with animals and permitted to have free contact to water at libitum. The guiding principle of the Institutional animal ethical committee which was approved by the university (UNISZA/AEC/14/007) and the current ethical norms was followed to conduct the experiments on test animals.

Stimulation of diabetes in the rats

Newly prepared solution of STZ (50 mg/kg b w) in 0.1 M citrate buffer (pH 4.5) was injected through intraperitoneal route in the overnight fasted male Wistar rats for the stimulation of diabetes. After 72 h of injection, the elevated plasma glucose levels confirmed the animals were in diabetic condition. Rats were monitored with unvarying glycosuria and hyperglycemia (blood glucose >8.1 mmol/L) throughout the study.

Design of the Study

Totally twenty four male rats were randomly taken into six animals in each four groups (G):

G- I: The rats treated with only drinking water for 10 days as normal control;

G- II: STZ induced rats;

G- III: 5 mg syringin/kg body weight was treated daily with G-II rats;

G- IV: 50 mg metformin /kg body weight was treated daily with G-II rats.

After 24 hrs all animals were sacrificed using halothane after dosage administration of the extract and distilled water.

Preparation of serum

The method for serum preparation was explained by Yakubu *et al*. (2006. By using halothane anesthesia, the cervical region of the rats was rapidly bald to exposé the jugular veins. To avoid blood contamination by interstitial fluid the jugular veins were slightly displaced. The veins were sharply incised through sterilized carving knife and an aliquot (2mL) of the blood was collected into a centrifuged tubes containing EDTA sample (BD Diagnostics, preanalytical systems, Midrand, USA) for the hematological investigation. An added 5mL of the blood was allowed to coagulate for 10 min at room temperature and then centrifuged at 1500 g for 5 min with Hermle B ench Top Centrifuge (Model Hermle, Z300, Hamburg, Germany). Using the Pasteur pipettes the serum was collected and aspirated into sample bottles and used within 12 h of preparation for the assay.

Plasma glucose and hematological parameters

Levels of Fasting Blood Glucose (FBG) were measured at 0, 5 and 10th day with modified glucose oxidase - peroxidase method (Trinder, 1969). To determine the hematological parameters such as red blood cells (RBC) and its related indices, Horiba ABX 80 Diagnostics (ABX pentra Montpellier, France) was used and the manufacturer's instruction was followed. White blood cell (WBC), neutrophils, monocytes, lymphocytes, eosinophils, basophils and platelets were also analyzed. Hematological parameters like hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV), red cell distribution width (RCDW) were determined.

Physiological criterions of DM

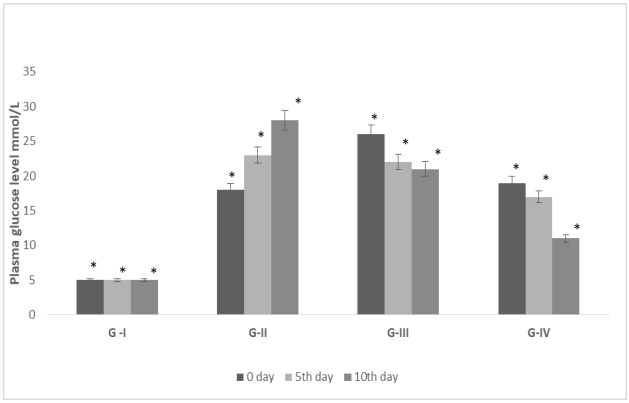
Every day feed and water intakes were measured during the experimental periods, simultaneously the body weight of the animals were also measured on 0, 5th and 10th day.

STATISTICAL ANALYSIS

All the data were statistically analyzed with SPSS 17.1 software. 'One-way analysis of variance' followed by 'least significant difference test' was used for the hypothesis testing methods. To indicate the statistical significance a value of $P<0.05$ was considered. A mean ± SEM was expressed from the results obtained in each group.

RESULTS

The level of total plasma glucose in each group from G-I to G-IV was shown in fig. 1. When compared with normal rats the STZ injected Wistar rats showed significant increase in the levels of blood sugar due to the significant diabetogenic response. In the case of orally administered rats with syringin, the level of blood glucose was reduced significantly ($P<0.05$) as evaluated with G-II rats. The data acquired at G-III contrasted positively well through that of G-IV rats.



*:P<0.05 as compared with diabetic control group.

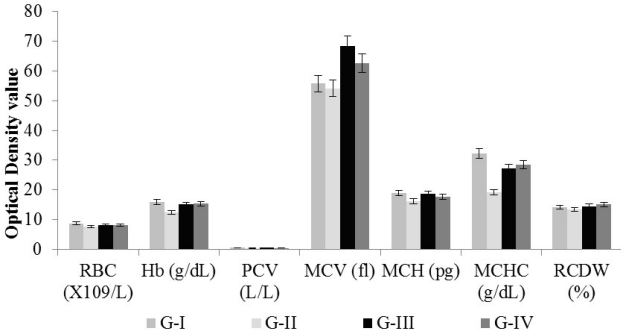
Fig. 1: Effect of syringin on plasma glucose level.

In G-II rats the levels of Red Blood Cell (RBC), Hemoglobin (Hgb), Packed Cell Volume (PCV), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV) and Red Cell Distribution Width (RCDW) were significantly decreased. In the case of G-III and G-IV rats the above mentioned hematological parameters were drastically increased (fig. 2).

Table 1: The effect of syringin on WBC and its differentials

Parameters	G-I	G-II	G-III	G-IV
WBC ($X10^9$/L)	17.00 ± 3.20	2.53 ± 0.93[a]	6.96 ± 2.03[b]	6.00 ± 5.60[b]
Neutrophils (%)	25.37 ± 1.17	2.59 ± 0.51[a]	19.80 ± 0.01[b]	23.30± 0.16[b]
Monocytes (%)	17.46 ± 6.11	4.69 ± 1.00[a]	14.70 ± 0.41[b]	19.00± 0.64[b]
Lymphocyte (%)	65.40 ± 6.86	5.36 ±0.33[a]	60.90 ± 2.20[b]	61.40± 5.10[b]
Eosinophil (%)	5.70 ± 1.18	1.03 ± 0.78[a]	4.50 ± 0.22[b]	1.20 ± 0.32[b]
Basophils (%)	0.53 ± 0.21	0.03 ± 0.03[a]	0.10 ± 0.02[b]	0.25 ± 0.15[b]
Platelets ($X10^9$)	851.00±78.58	55.00±31.11[a]	201.00±68.00[b]	176.00± 55.20[b]

a: P <0.05 vs control group; b: P <0.05 vs diabetes group.



Values are statistically significant from normal and treated groups * p< 0.05.

Fig. 2: The effect of syringin on RBC and its differentials.

Table 2: Effect of syringin on food intake in grams.

Treatment	Initial	Final
G-I	24.08 ± 2.50	30.53 ± 1.46
G-II	40.37 ± 2.38	59.29 ± 6.41
G-III	40.46 ± 4.09	34.69 ± 2.73
G-IV	41.40 ± 5.49	32.36 ±1.57

a: P <0.05 vs control group; b: P <0.05 vs diabetes group.

Table 3: Effect of syringin on the fluid intake

Treatment	Initial (ml)	Final (ml)
G-I	30.21 ± 1.24	34.73 ± 4.63
G-II	60.37 ± 4.56 [a]	71.29 ± 5.18 [a]
G-III	60.46 ± 3.91 [b]	39.69 ± 2.24 [b]
G-IV	59.40 ± 6.30 [b]	37.36 ±6.41 [b]

a: P <0.05 vs control group; b: P <0.05 vs diabetes group.

The total levels of serum WBC, lymphocytes, monocytes basophils, neutrophils and eosinophils were shown in table 1. The syringin injected rats showed slightly increased WBC level when compared with the G-II. Due to the effect of syringin the level of lymphocyte, eosinophils, monocytes and platelets were significantly increased however did not alter the basophils level.

Throughout the study period the feed and water intake of the G-II rats were increased as compared with G-I. However, after syringin injection, the feed and water intake was clearly decreased in G-III as compared with the diabetic untreated rats G-II was represented graphically (table 2 and 3).

Table 4: Effect of oral administration of syringin on body weight in gms

Treatment	Initial	Final
G-I	160.45 ± 3.57	220.62 ± 2.75
G-II	158.13 ± 4.82 [a]	131.54 ± 3.29 [a]
G-III	155.51 ± 5.27 [b]	180.23 ± 4.63 [b]
G-IV	183.26 ± 7.19 [b]	190.40 ±3.15 [b]

a: P <0.05 vs control group; b: P <0.05 vs diabetes group.

The body weights of diabetic animals induced with STZ were significantly decreased (G-II). The syringin administered rats distinctly improved in their body weight (G-III) were shown in (table 4) as compared with the initial body weight.

Table 5: Effect of syringin on plasma insulin level

Group	Insulin (µU/ml) At 10^{th} day
G-I	55.01 ± 3.70
G-II	39.13 ± 4.82 [a]
G-III	51.51 ± 5.17 [b]
G-IV	54.26 ± 4.19 [b]

a: P <0.05 vs control group; b: P <0.05 vs diabetes group.

DISCUSSION

STZ is utilized as a mediator to tempt DM via specific cytotoxicity consequence taking place pancreatic β cells. Therefore it changes endogenous insulin liberate and as an outcome raised blood glucose level (Nastaran, 2011). The nonstop application of syringin or metformin for 10 days considerably abridged the blood glucose level in STZ stimulated diabetic rats (G-III and G-IV).

Metformin's effectiveness, precautions profile, useful cardiovascular and metabolic effects all along with its capability to be connected through added antidiabetic agents makes this drug the first glucose lowering mediator of option when treating patients through T2DM. It acts as a matter of first importance at the liver by decreasing glucose yield and, secondarily, by enhancing glucose take-up in the minimal tissues, essentially in muscle

(Nastaran, 2011). Therefore, in the current investigation, metformin was utilized as a typical drug to contrast the effectiveness of syringin.

The measurement of hematological factors could be used to expose the harmful cause of unknown compounds with plant extracts as well as various phytochemicals on the blood components of animals. They also used to decide feasible modifications in the levels of biomolecules such as hematology, metabolic products, enzymes, histomorphology and normal functioning of the organs (Bedoya *et al.*, 1996).

The incidence of anemia in DM has been accounted due to the augmented non-enzymatic glycosylation of RBC covering proteins (Magalhães *et al.*, 2008). These Protein Oxidation and hyperglycemia in DM leads to an increase in the formation of lipid peroxides that direct to hemolysis of RBC. In this investigation, in diabetic rats the levels of lipid peroxide present in the RBC were not calculated. Though, the RBC parameters such as Hemoglobin (Hgb), Packed Cell Volume (PCV), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV) and Red Cell Distribution Width (RCDW) were considered to examine the favorable effect of syringin on the anemic position of the DM rats. The intensities of Hgb, RBC, PCV, MCH and MCHC in the G-II were severely decreased which may be endorsed to the infections on the regular body systems. This surveillance approves with report of Baskar *et al*. (2006) who described antihyperglycemic action of aqueous root extract of *Rubia cordifolia* in STZ persuaded DM rats. The adjustments of these parameters are well recognized to cause anemic disorder in man (Oyedemi *et al.*, 2011). Subsequent syringin dosages, the number of RBC and its associated indices were substantially upgraded in G-III. This gives a sign that syringin may encourage the creation or ooze of erythropoietin in the stem cells of the animals. The synthesis of RBC was regulated by a glycoprotein hormone such as Erythropoietin by induction of bone marrow cells. (Ohlsson *et al*, 2014). The stimulation of this hormone improves quick production of RBC which is reinforced by the enhanced level of MCH and MCHC (Shenoy and Goyal, 2002). These parameters are utilized measurably to express the concentration of Hgb and to prescribe the renovation of oxygen carrying capacity of the blood; nonetheless, the deed system of syringin isn't analyzed in this investigation. Though, it may be recognized to the ability of syringin to poorer lipid peroxidation (LPO) level that reasons hemolysis of RBC (Balasubramanian *et al.*, 2009; Faure *et al.*, 1991), hence, could inhibit LPO of polyunsaturated fatty acids in the cell membrane and hemolysis of RBC in the DM animals stated by Torell and Faure *et al* (1986).

STZ is an antibiotic that suppresses the immune system by destructing WBC cause destruction to pancreatic β cells. The WBC count and its differentials were significantly reduced in the STZ injected rats. The reduction of these parameters could be related to suppression of leukocytosis from the bone marrow which may account for meager defensive mechanisms against infection. Consequentially, they might have effects on the immune system and phagocytic action of the animals (Dahlbäck, 2008). The WBC and its associated indices were notably restored to near normal following syringin administration. Thus syringin with capability to induce the formation of white blood count may perhaps be accountable for the experimental outcome in the treated rats (Rao *et al.,* 2016). The levels of WBC, monocytes, lymphocytes, eosinophils and neutrophils were significantly better in syringin group as compared with metformin treated group. In the current investigation there was no impact on basophils in the syringin injected rats.

Platelet total limit was exposed in DM tolerant with dependable denied glycemic control brought about by need or shortage of insulin (Baskar *et al*., 2006). Platelets said to be thrombocytes assist to arbitrate blood coagulating, which is a meshwork of fibrin strands. The blood will be ceased by the arrangement of strands at any vascular opening. It plays a basic position in fixing of vascular damage and decrease of blood misfortune (Dahlbäck, 2008). The diminished dimension of platelets in DM rodents initiated with STZ was affirmed in this investigation in connection to the G-I rodents. Long haul decrease of this parameter may result in inside and outer drain and ultimately prompts casualty. Be that as it may, after syringin organization, the dimension of platelet was improved unmistakably as contrasted and G-II rodents. This impact demonstrated the ability of the syringin to induce the biosynthesis of thickening components as bolstered by other analyst Adebayo OJ with *Bougainvillea spectabilis* leaves (Adebayo *et al*., 2005) theorized that the event of dynamic intensify that may help to accelerate blood coagulation or coagulating, especially during extreme blood loss or hemorrhage.

At the point when contrasted and the G-I rodents the feed and water intake of the G-II rodents were essentially expanded. These indications are all around recognized markers of T2DM in similarly human and creature models which are through impact of insulin lack (Baily *et al.,* 1985). In G-III the feed intake was fundamentally decreased after organization of syringin. In G-II creatures the water admission of was significantly higher when contrasted and G-III and G-IV rodents. These outcomes were identified with the report of Kim *et al* (2006) who affirmed the impact of *Morus alba* in controlling the desire for sustenance and water consumption under diabetic condition. There will be a noteworthy diminishing in the body loads (28-33 g) of G-II creatures after enlistment of STZ into the creatures watched for 10 days. The misfortune in the body weight of the unhealthy creatures concurs with the finding of Oyedemi *et al* (Oyedemi *et al.,* 2011) who watched comparable impact

on DM creatures instigated with STZ. The misfortune in body weight has been connected with corruption of auxiliary proteins and muscle squandering. Oral organization of syringin had the option to improve the body weight of the creatures. The outcome demonstrated that syringin had the capacity of overseeing glucose level just as controlling muscle squandering and instigated adipogenesis.

CONCLUSION

In conclusion, the statistical data obtained in this study hypothesizes that syringin possesses antihyperglycemic property as well as prevents various complications of diabetes and ameliorating some hematological parameters as discussed. Further experimental investigation is also needed to explore the relevant therapeutic effect to substantiate its ethno medicinal usage.

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