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IN VIVO EVALUATION OF ANTIDIABETIC PROPERTIES OF CAFFEIC ACID, SALVIANOLIC ACID AND VANADIUM PENTOXIDE IN SWISS ALBINO MICE

G. Rajalakshmi[1*] and R. Malathi[2]*

[1]Department of Biotechnology, Hindusthan College of Arts and Science, Coimbatore – 641028.
[2]Department of Genetics, Madras University, Chennai – 600004.

***Corresponding Author: Dr. R. Malathi**
Professor and Head, Department of Genetics, Madras University, Chennai – 600004.

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ABSTRACT
Diabetes is the metabolic disorder which is classified into type 1 (in which body does not produce enough insulin) or type 2 (because cells do not respond to insulin that is produced). Type 2 diabetes has progressed beyond the point where it can simply be considered a medical problem and hence the present study was carried out to determine how the chosen compounds elicit anti diabetic response in Streptozotocin (STZ) induced Swiss albino mice. 36 animals were divided into six groups *viz.*, control, STZ induced, STZ + positive control (glibenclamide) and treated groups of the three compounds (caffeic acid, salvianolic acid and vanadium pentoxide), with six animals in each group. Biochemical parameters were analysed and the results were interpreted for control and treated groups. STZ induced diabetic mice lowered the body weight of animals as they interrupted with the feeding of mice whereas the animals in treated group could lower blood glucose and help to gain body weight in animals injected with STZ. Caffeic acid has good potential to reduce blood sugar when compared to salvianolic acid and vanadium pentoxide.

KEYWORDS: STZ, caffeic acid, blood glucose, serum cholesterol, salvianolic acid, vanadium pentoxide.

INTRODUCTION

Diabetes, a chronic metabolic disease, occurs when the beta cells of pancreas fails to produce enough insulin (Type I diabetes) or when the body is unable to effectively utilize the insulin it produces (Type 2 diabetes). More than 80% of diabetes deaths occur in under developed and developing countries. It has been projected that diabetes will be the 7th leading cause of death in 2030 (WHO, 2012). Abnormalities in glucose and lipid metabolism due to oxidative stress results in hyperglycemia and dyslipidemia. Hyperglycemia involves complications like retinopathy, nephropathy, neuropathy and cardiovascular diseases (Almeida *et al.*, 2012; Hussain and Gobba, 2013).

Several therapeutic strategies are currently available for the treatment of this chronic metabolic disorder. Complementary and alternative medicine applications have attracted special attention in recent research for they offer new promising opportunities for the development of efficient, side-effect free and lower cost alternatives to existing synthetic hypoglycemic agents (Mukherjee *et al.*, 2010).

Caffeic acid the main representative of the hydroxycinnamic and phenolic acids is found abundant in fruits, vegetables, coffee, tea, wine, grains and Chinese medicinal herbs that account for about a third of phenolic compounds in our diet (Sakakibara H, *et al.*,2003; Jiang *et al*, 2005). Salvianolic acid is a polyphenolic compound isolated from the root of Salvia Miltiorrhiza Bunge, which is a traditional Chinese medicine and widely used in the Asian countries for the treatment of cardiovascular disease and diabetes (Qiang *et al.*, 2015).

Vanadium, member of transition series of element is the most abundant element in earth's crust. Its requirement in lower organisms has been found and its value in humans is under study. Vanadium requirement in human body is estimated to be 10 - 160µg (Pathak and Lahkar, 2015). Very few reports are available on anti – diabetic properties of vanadium pentoxide, it's anti – angiogenic potential has to be unraveled.

The present study was aimed to determine the efficacy of phenolic compounds and trace element, vanadium in lowering blood glucose and cholesterol in diabetes induced Swiss albino mice models.

MATERIALS AND METHODS

Selection of animals for study
↓
Acclimatization in laboratory conditions
↓
Choice of feed, supply of water and feed *ad libitum*
↓
Determination of dosage of test drugs by LD50 analysis
↓
Administration of standard and test drugs to the animals
↓
Determination of body weight, blood sugar and cholesterol profile every 7 days from 0^{th} day
↓
Statistical analysis to compare control and treated groups

The animal chosen for study was Swiss albino mice. The study was divided into six groups with six animals in each group (n= 6). The animals were housed in the Pharmacology Department of KMCH College of Pharmacy, Coimbatore. They were acclimatized to the laboratory conditions and fed with feed and water *ad libitum.*

The animals were administered with streptozotocin along with extracts and one group with positive control for a period of 21 days. Body weight of the mice, blood sugar and cholesterol; profile was checked at 0, 7, 14, 21 and 28 days. The Streptozotocin was administered as a multiple dose of 40 mg/kg in mice for 5 consecutive days to induce diabetes. The mice were treated with caffeic acid (10mg/kg), salvianolic acid (3mg/kg), vanadium pentoxide (10mg/kg) and positive control – glibenclamide (5mg/kg) of body weight for 21 days followed by streptozotocin injection.

For determining body weight of mice in control, diabetes induced and treated groups, the mice were weighed using electronic weighing balance (Shimadzu, Japan). Blood samples were collected from the tip of mice tail vein and Glucose levels were estimated using a glucose oxidase-peroxidase reactive strips and a glucometer (Accu-chek, Roche Diagnostics, USA). After 21 days, the mice were sacrificed and blood sample collected. Serum was separated and subjected to cholesterol profiling using enzymatic PAP method (Roche diagnostics Kit). The estimation studies were carried out using the protocol described in Maduka *et al.*, 2015.

Statistical analysis was performed using SPSS software (version 15.0). For better comparison means ±SD is shown. The correlation between variables was examined by estimating the Spearman's correlation coefficient.

RESULTS AND DISCUSSION

The results obtained were compiled and the data were tabulated for body weight, blood sugar and cholesterol parameters of control and treated groups (Table 1, 2 and 3). The effects of Caffeic acid, Salvianolic acid and Vanadium pentoxide were comparatively analysed and presented graphically (Figure 1, 2 and 3). Caffeic acid could significantly lower blood glucose level followed by Salvianolic acid and vanadium pentoxide. This was in accordance with the previous findings (Mohammed *et al.*, 2015; Pathak and Lahkar 2015). The results were subjected to statistical analysis.

From Table 1, the body weights of the animals in six groups were deduced as follows. The initial body weight in all the groups were found to be between 28.10±0.98 to 32.17±2.32 which was found to be increased in group III, IV, V and VI treated groups. Group II (STZ induced showed a decrease in body weight of the animals as the animal could not feed and Group IV has shown significant increase in body weight (33.33± 3.27) followed by Group V (32.83± 3.49) and Group VI (32.00 ± 2.61). Comparatively, body weight was found to be reduced in group III (positive control group) which was recorded as 30.33±1.86.

This is in accordance with the results of previous findings (Mishra *et al.*, 2012; Hussain and Gobba, 2013). STZ – induced diabetes is characterised by body weight loss and treatment with CAMBA, amide derivative of caffeic acid could significantly normalise body weight of study groups.

Table 2 gives a report of blood sugar in the control and treated groups. The initial blood glucose level was found to be in between 111.83±8.66 to 142.67±23.58 which was found to be reduced in treated groups. Reduction in group IV was found to be 102.67±38.18 followed by group V and VI which recorded 140.83±37.42 and 166.00±15.78 respectively.

Recent research has shown that caffeic acid decreased blood concentration and increased insulin release in diabetic rats. Caffeic acid is demonstrated to have pharmacological importance in treating Type 2 diabetes (Mohammed *et al.*, 2015). Insulino – mimetic effects of vanadium pentoxide was reported by Pathak and Lahkar (2015) where STZ induced diabetes rats when treated with vanadium pentoxide lowered blood glucose level.

The cholesterol profile of the animals in control and treated groups are tabulated in Table 3. In STZ induced

diabetes the raise in blood glucose is accompanied by an increase of LDL and VLDL cholesterol and decrease in the HDL cholesterol. Total cholesterol amounts to 259.12 ± 2.22. Triglycerides and free fatty acid values were also found to be increased to 43.00 ± 3.29 and125.52 ± 7.62 respectively. Decrease in LDL, VLDL and increase in HDL was noted in treated groups. Group IV recorded 70.22 ± 5.42, 13.27 ± 1.81 and 61.08 ± 4.04 of total cholesterol, triglycerides and free fatty acids correspondingly.

It has been reported that caffeic acid could lower LDL and increase HDL cholesterol which could help in preventing diabetic complications and improving lipid metabolism in diabetics (Shivajothi *et al.*, 2008). Salvianolic acid B could lower LDL and VLDL levels in treated mice upto two fold has been reported (Safoura Raoufi *et al.*, 2015).Vanadium pentoxide has shown to stimulate lipogenesis as well as inhibition of lipolysis and gluconeogeneis in diabetic rats (Pathak and Lahar, 2015).

Table: 1 Body weight

Groups	Initial body weight	After 72 hours Body weight	Body weight 1st week	Body weight 2nd week	Body weight 3rd week	Body weight 4th week
Group I (Control)	28.17 ± 0.98	28.67 ± 1.03	28.50 ± 1.38	28.67 ± 0.82	28.83 ± 1.72	29.00 ± 1.90
Group II (STZ induced)	28.33 ± 0.52	30.83 ± 0.98	27.60 ± 2.19	28.60 ± 2.30	29.00 ± 0.71	28.00 ± 2.55
Group III (STZ + Glibenclamide)	31.17 ± 2.14	31.83 ± 2.71	32.67 ± 4.18	34.33 ± 3.88	30.50 ± 1.38	30.33 ± 1.86
Group IV (STZ + Caffeic acid)	32.17 ± 2.32	32.33 ± 3.67	33.17 ± 3.82	35.00 ± 4.69	29.50 ± 1.64	33.33 ± 3.27
Group V (STZ + Salvianolic acid)	31.50 ± 2.43	31.33 ± 2.07	33.17 ± 3.13	34.50 ± 2.74	31.00 ± 1.67	32.83 ± 3.49
Group VI (STZ + Vanadium Pentoxide)	30.50 ± 1.38	32.00 ± 1.67	30.50 ± 1.38	32.17 ± 2.40	29.67 ± 1.37	32.00 ± 2.61
SEd	2.62155					
CD (P<0.05)	5.17294					

Values are mean ± SD of six samples in each group.

Data of the present study implies that there is a significant decrease in blood sugar levels.

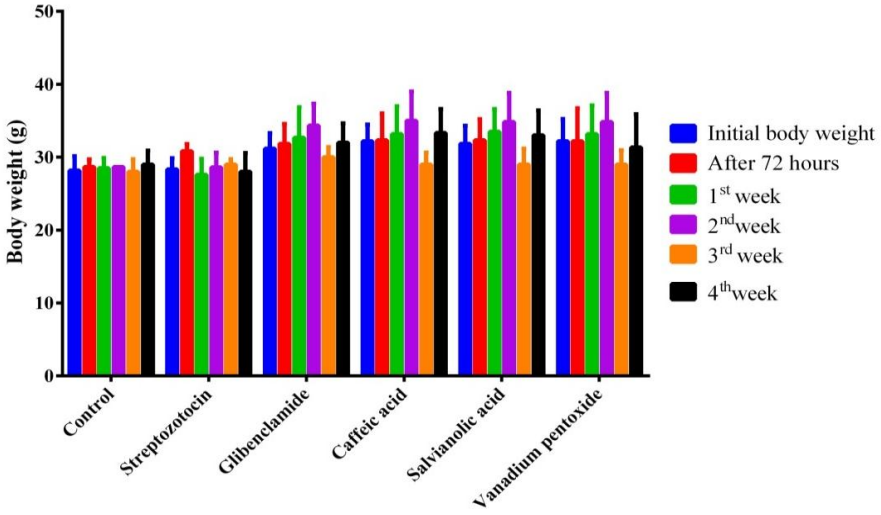

Fig: 1. Body weight of treated mice

Tables: 2 Blood Sugar

Groups	Initial Blood fasting sugar	After 72 hours Fasting Blood Sugar	Fasting Blood sugar 1st week	Fasting Blood sugar 2nd week	Fasting Blood sugar 3rd week	Fasting Blood sugar 4th week
Group I (Control)	119.67 ± 12.26	113.33 ± 24.04	87.33 ± 18.36	88.83 ± 17.53	109.00 ± 11.75	74.00 ± 8.15
Group II (STZ induced)	142.67 ± 23.58	253.17 ± 19.50	280.00 ± 13.60	357.40 ± 14.36	360.00 ± 17.51	366.60 ± 30.39
Group III (STZ + Glibenclamide)	137.33 ± 19.65	244.67 ± 30.98	234.33 ± 25.37	185.17 ± 16.41	175.50 ± 29.43	175.50 ± 29.43
Group IV (STZ + Caffeic acid)	111.83 ± 8.66	230.83 ± 7.91	202.00 ± 17.38	175.00 ± 16.38	162.00 ± 24.80	102.67 ± 38.18
Group V (STZ + Salvianolic acid)	115.17 ± 27.57	236.33 ± 33.53	205.67 ± 38.46	187.50 ± 35.64	158.17 ± 18.99	140.83 ± 37.42
Group VI (STZ + Vanadium Pentoxide)	113.50 ± 6.66	270.83 ± 41.19	241.00 ± 37.65	192.00 ± 54.01	182.17 ± 11.62	166.00 ± 15.78
SEd	35.82175					
CD (P<0.05)	70.68476					

Values are mean ± SD of six samples in each group.

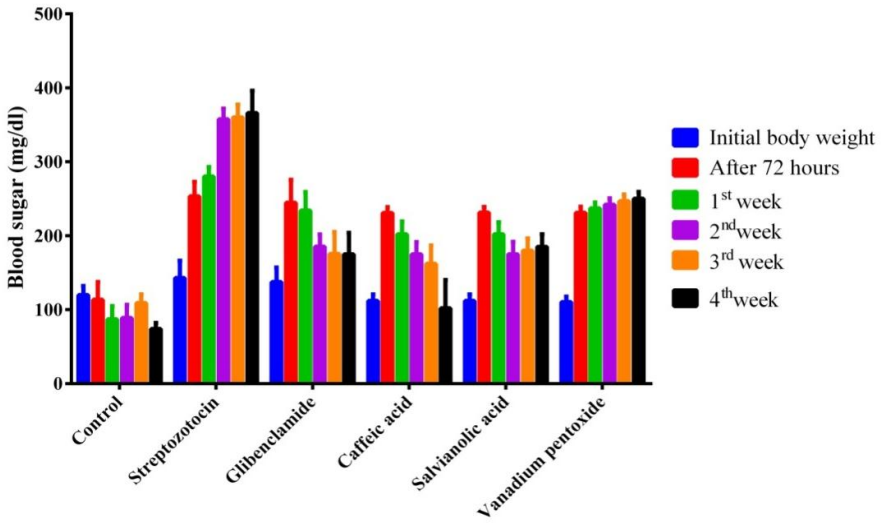

Fig: 2. Blood sugar level of treated mice

TABLE: 3 Cholesterol profiling of Control, STZ induced and treated groups

Groups	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	Free fatty acids (mg/dl)
Normal	86.52 ± 4.38	15.18 ± 1.31	60.22 ± 2.78
Diabetic control	259.12 ± 2.22	43.00 ± 3.29	125.52 ± 7.62
STZ + Glibenclamide	79.24 ± 5.85	13.72 ± 1.05	64.27 ± 5.02
STZ + Caffeic acid	70.22 ± 5.42	13.27 ± 1.81	61.08 ± 4.04
STZ + Salvianolic acid	88.68 ± 6.78	19.52 ± 1.44	52.24 ± 4.14
STZ + Vanadium pentoxide	99.63 ± 7.92	26.65 ± 1.92	66.85 ± 4.92

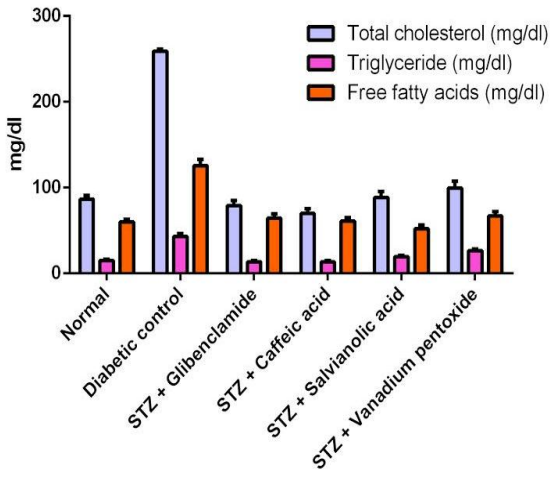

Fig: 3 Cholesterol profiling of treated mice

CONCLUSION

From the present study, significant reduction in blood glucose levels and cholesterol levels were noted in treated mice groups. When compared to positive control glibenclamide, increase in rate of metabolism of blood sugar was noted in caffeic acid treated mice. In treatment of diabetes, caffeic acid, salvianolic acid and vanadium pentoxide can be used as they have a promising role in decreasing blood glucose levels. Also, Caffeic acid seem to lower cholesterol levels and hence can be used to treat diabetic complications related heart disorders.

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