



## ORIGINAL ARTICLE

# Antihyperglycemic Effect of *Pimpinella Tirupatiensis* Leaves in Streptozotocin-Induced Diabetic Rats

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### ABSTRACT

Herbal therapies are commonly used to treat or manage various diseases including diabetes mellitus. *Pimpinella tirupatiensis* is Indian traditional medicine and the plant has been a popular remedy for various diseases such as antitumor genic, antimicrobial, purgative, analgesic, antiseptic, antipyretic and anti-inflammatory. The current study was intended to evaluate the antidiabetic efficacy of ethyl acetate extract of *Pimpinella tirupatiensis* leaves in streptozotocin-induced diabetic rats. Diabetes was induced in male Sprague-Dawley rats by the administration of streptozotocin (55mg/kg body weight) intraperitoneally. *Pimpinella tirupatiensis* extract was administered to diabetic rats for 4 weeks. The extract effect (500 mg/kg body weight) on serum glucose level, lipid profiles, serum aminotransferase (AST, ALT and ALP), creatinine, urea levels, body weight and also physiological parameters (food and water intake) were studied in diabetic rats. The serum glucose levels, lipid profiles (triglycerides and total cholesterol), serum aminotransferase (aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP)), creatinine and urea levels in streptozotocin-induced diabetic rats, were significantly ( $P < 0.05$ ) normalized after 4 weeks of *Pimpinella tirupatiensis* extract treatment. Furthermore, the body weight improved obviously in diabetic rats treated with *Pimpinella tirupatiensis*. Continuous treatment by administering *Pimpinella tirupatiensis* ethyl acetate extract (500 mg/kg b.w) orally to diabetic rats for 4 weeks reversed physiological parameters (food and water intake) and all the above-mentioned biochemical parameter changes in a noteworthy ( $P < 0.05$ ) manner. This asserts that *Pimpinella tirupatiensis* ethyl acetate extract, which is efficacious in streptozotocin-induced diabetic rats, shall certainly be highly helpful in diabetes mellitus.

**Keywords:** *Pimpinella tirupatiensis*, STZ, lipid profiles, biochemical parameters, rat.

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### INTRODUCTION

Diabetes mellitus is one of the chronic metabolic disorder, is mainly linked to abnormal blood insulin levels or insensitivity of target organs to insulin [15]. The disease is associated with reduction in the quality of life augmented risk factors for mortality and morbidity. The chronic hyperglycemia is responsible in the development and progression of several complications, such as neuropathy, nephropathy, cardiovascular, cerebrovascular diseases and diabetic foot diseases [8,33]. In modern synthetic antidiabetic drugs, no satisfactory effective therapy is available to manage the diabetes mellitus till now. Though insulin therapy is also used to manage diabetes mellitus, several drawbacks were observed even after treatment like insulin resistance [28] hypoglycemic coma and hepatorenal disturbances [13,34], anorexia nervosa, brain atrophy and fatty liver [37]. Scientists are keenly interested to search a suitable low-cost active antidiabetic agent with minimum side effects. The only safe and reliable source is herbal remedy because it is non-toxic [19,22].

*Pimpinella tirupatiensis* is an endemic species distributed on Tirumala Hills (1000meters above the sea level of Chittoor district, Andhra Pradesh, India) [3,25] is one such plant Indian traditional medicine and the plant has been a popular remedy for various diseases such as antitumor genic, antimicrobial,

purgative, abortifacient, analgesic, antiseptic, antipyretic and anti-inflammatory [27]. The present study was undertaken to scientifically investigate its beneficial utility in diabetes mellitus.

## MATERIALS AND METHODS

### Plant Material and Preparation of Extraction

*Pimpinella tirupatiensis* leaves were collected from Tirumala Hills of Seshachalam range of Eastern Ghats and identified by the taxonomist of herbarium Dept. of Botany, S.V. University, Tirupati Andhra Pradesh, India. Fresh leaves of *Pimpinella tirupatiensis* were dried at room temperature for 24 hours and subjected to 40°C for a week to dry completely. The dried leaves were finely powdered by using commercial grinder for 5 minutes. Then, plant powder was soaked in organic solvent (ethyl acetate) sequentially for 24 hours up to 72 hours. The extract was filtered using filter paper Whatman no. 1 before being dried under reduced pressure in rotary evaporator to give a green colored extract.

### Selection of Animals

Male Sprague-Dawley rats, (weight: 190 ± 200 g) were used for this study, obtained from the Indian Institute of Science, Bangalore were used in this study. All the rats were maintained in the polypropylene cages (six rats per cage), at an ambient temperature of 25 ± 2 °C with 12-h-light/12-h-dark cycle. Rats were allowed free access to standard chow and water *ad libitum* during the study. All the experiments in this study were performed according to the regulations and this study was approved by the Institutional Animal Ethical Committee and its resolution number; 09 (ii)/a/CPCSCA/IAEC/07-08/SVU/Zool/ dated 26/6/08.

### Chemicals

Streptozotocin and glibenclamide were obtained from Sigma chemicals (USA). The assay kits for glucose levels, lipid profiles (triglycerides and total cholesterol), liver biomarkers enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP)) creatinine and urea were purchased from instrumentation laboratory company- Lexington, MA 02421-3125 (USA). All the other chemicals were analytical grade.

### Induction of Diabetes

The animals were starved for overnight and diabetes was induced by a single intraperitoneal injection of a freshly prepared solution of streptozotocin (55 mg/kg body weight) in 0.1M cold citrate buffer (pH 4.5) in a volume of 0.1ml/10g body weight [36]. The animals were allowed to drink 5% glucose solution 72 hours to overcome the streptozotocin- induced hyperglycemia.

### Experiments Time Lines

Four groups of rats containing six rats in each group were divided as follows. Group I: normal rats, Group II: diabetic control rats, Group III: Ethyl acetate extract of *Pimpinella tirupatiensis* (500 mg/kg/b.w) treated diabetic rats. Group IV: Glibenclamide (20 mg/kg/b.w) treated diabetic rats. The animals were anaesthetized with ether, and the fasting blood samples were collected every week through retro-orbital plexus puncture. This was put into serum tubes (BD Vacutainer® Plus plastic serum tube). The Blood samples were centrifuged at 1000 X g for 10 min and the supernatant obtained was used for assays of various biochemical examinations.

### Physiological Parameters

The general physical condition of each animal was observed during the experimental period. Food and water intake were measured daily and individual body weight was recorded weekly during the treatment period.

### Biochemical Assays of Serum

Serum biochemistry assays were performed using a Clinical chemistry system (ILAB 300 plus) for the following parameters: The serum glucose levels, lipid profiles (triglycerides and total cholesterol), activity of serum biomarkers enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP)), creatinine and urea levels.

### Statistical Analysis

Statistical analysis was performed using SPSS software package Version 14.0. The values were analysed by one-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test. All the results were expressed as mean±SEM for six rats in each group.  $P < 0.05$  were considered significant.

## RESULTS

### Physiological Parameters (Body Weight, Food and Water Intake)

A significant reduction in body weight was observed in diabetic rats when compared to control rats ( $P < 0.05$ ). Rise in body weight was observed in *Pimpinella tirupatiensis* extract treated diabetic rats when compared to control diabetic rats (Fig, 1).

Food intake was significantly ( $P < 0.05$ ) augmented in diabetic rats as compared with normal rats. On the other hand, water intake was significantly increased in diabetic rats as compared to normal rats. Treatment with extract of *Pimpinella tirupatiensis* brought down food and water intake in diabetic rats as compared with diabetic control rats (Fig 2, 3).

#### Effect of *Pimpinella Tirupatiensis* Ethyl Acetate Extracts on The Serum Glucose Levels

Fasting serum glucose levels of diabetic rats were significantly amplified as compared with that of the control ones ( $P < 0.05$ ). The enhanced fasting blood glucose levels in diabetic rats were significantly reduced with *Pimpinella tirupatiensis* treatment (Fig 4).

#### Effect of *Pimpinella Tirupatiensis* Ethyl Acetate Extracts on Serum Biomarker Enzymes

A significant raise of serum ALT and AST activity ( $P < 0.05$ ) was observed in streptozotocin-induced diabetic rats as compared to control group. Treatment of diabetic rats with extract resulted in a significant reduction in the activity of ALT and AST when compared to diabetic control rats. A significant augmentation in the activity ALP was observed in diabetic rats when compared control group. A significant decreased of serum marker enzymes activity of ALP was noticed due to the effect of extract as indicated in (Fig 5, 6, 7)

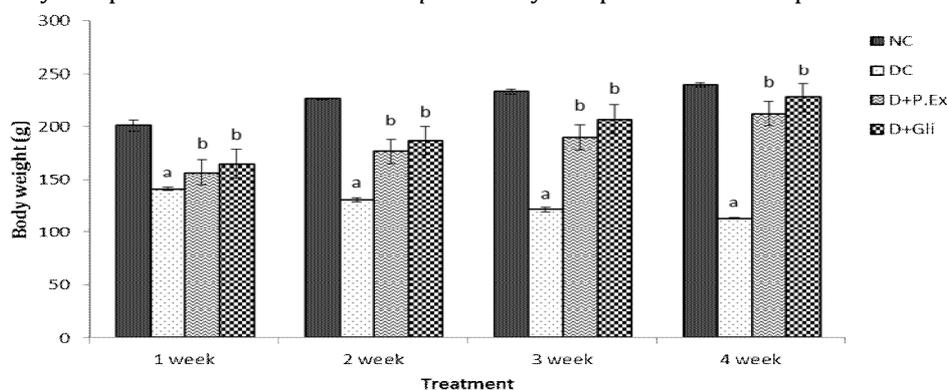
#### Effect of *Pimpinella Tirupatiensis* Ethyl Acetate Extracts on Serum Creatinine and Urea Levels

A significant amplified, creatinine and urea ( $P < 0.05$ ) levels were found in diabetic rats as compared with normal control rats. Treatment of diabetic rats with *Pimpinella tirupatiensis* extract resulted in a significant reduction in creatinine and urea levels as compared with diabetic control rats (Fig 8, 9).

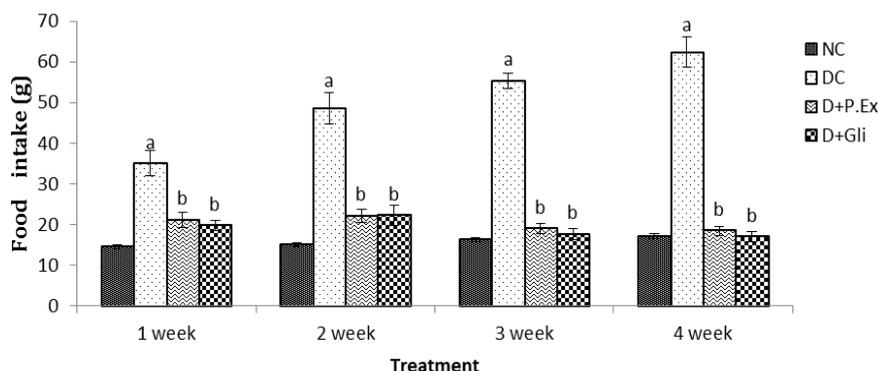
#### Effect of *Pimpinella Tirupatiensis* Ethyl Acetate Extracts on Serum Lipid Profiles

A significant augmentation in triglyceride, and total cholesterol ( $P < 0.05$ ) levels were observed in diabetic rats as compared to normal control. After treatment with extract there was a reduction in triglyceride and total cholesterol levels compared with diabetic rats. The continuous treatment with extract brought down the lipid profiles in diabetic rats to almost control levels as show in (Fig 10, 11)

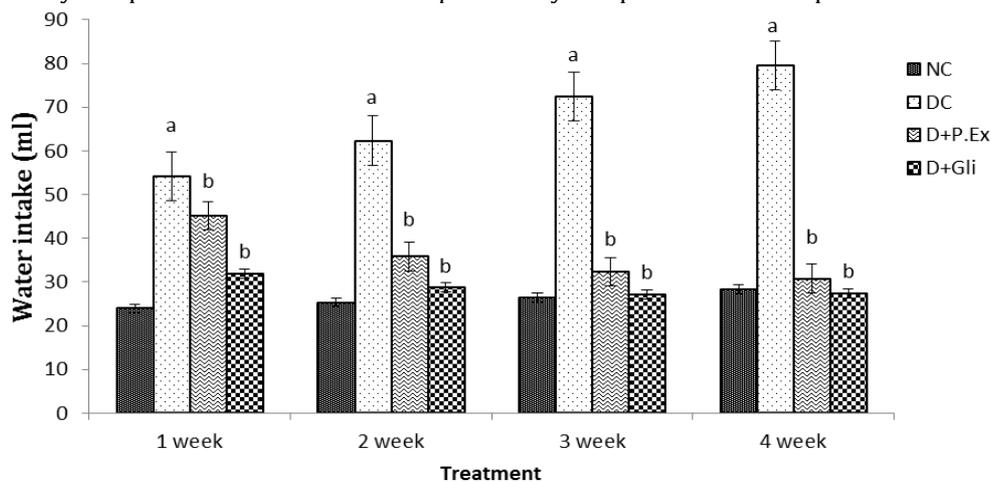
**Fig 1:** Effects of *Pimpinella tirupatiensis* extracts on body weight in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean  $\pm$  SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



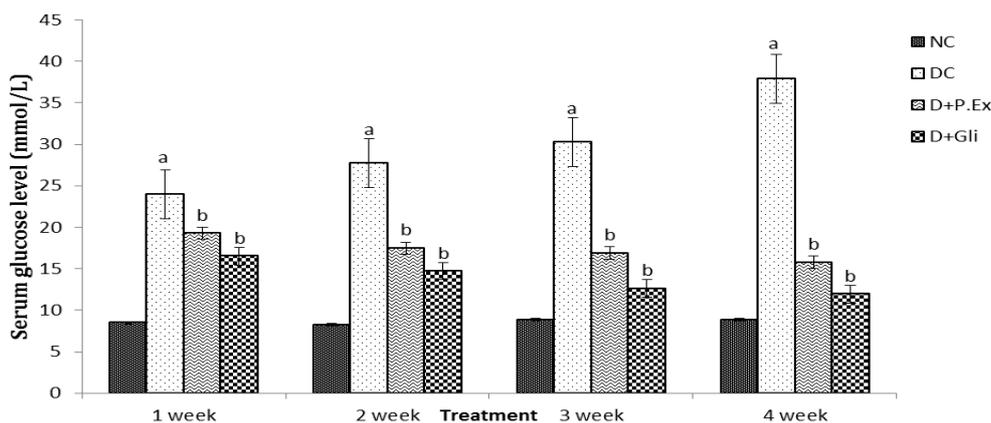
**Fig 2:** Effects of *Pimpinella tirupatiensis* extracts on food intake in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean  $\pm$  SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



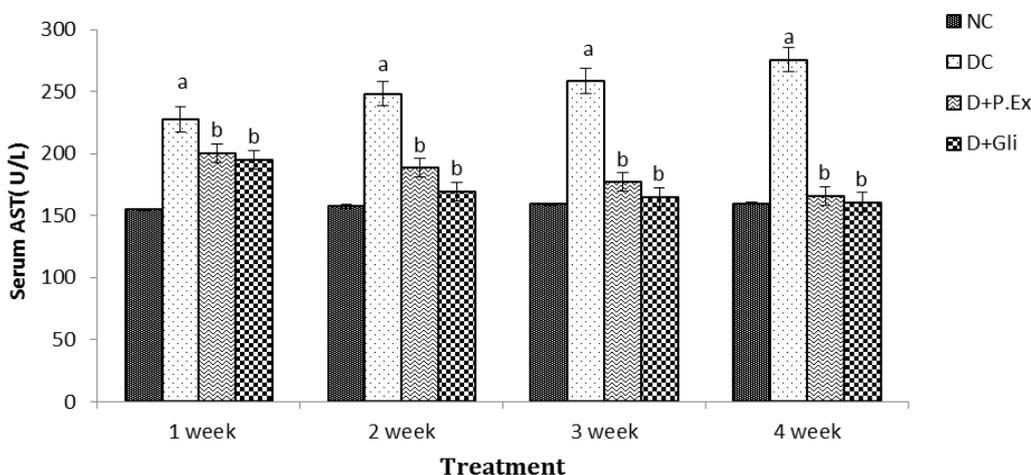
**Fig 3:** Effects of *Pimpinella tirupatiensis* extracts on water intake in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



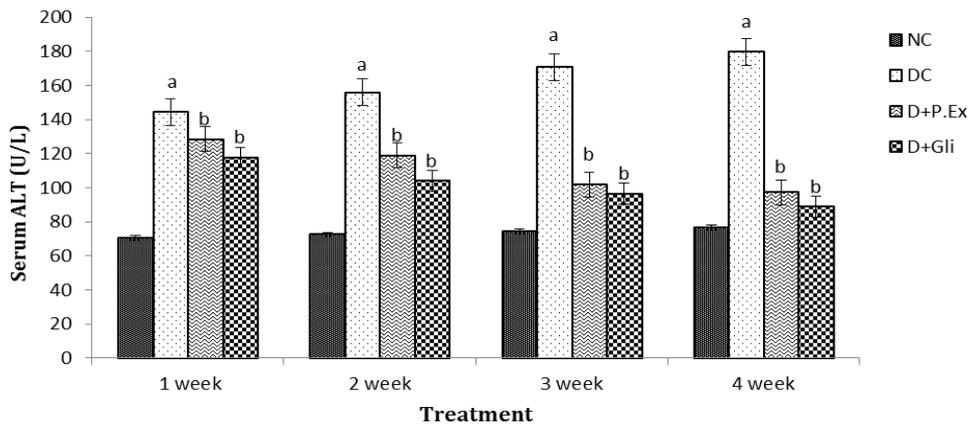
**Fig 4:** Effects of *Pimpinella tirupatiensis* extracts on serum glucose levels in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



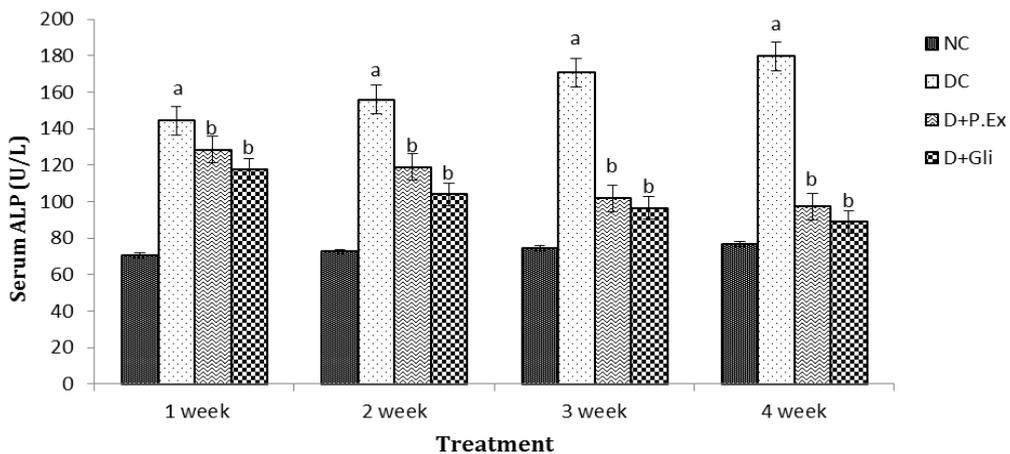
**Fig 5:** Effects of *Pimpinella tirupatiensis* extracts on serum AST activity in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



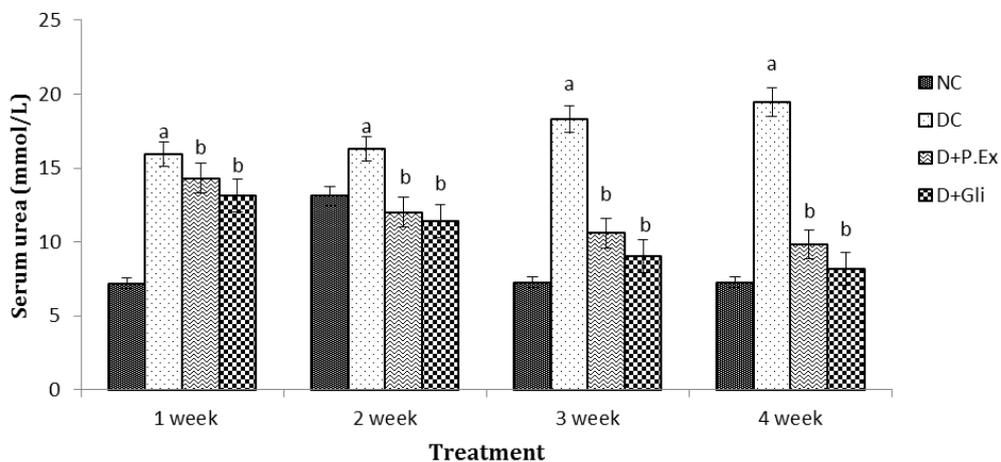
**Fig 6:** Effects of *Pimpinella tirupatiensis* extracts on serum ALT activity in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



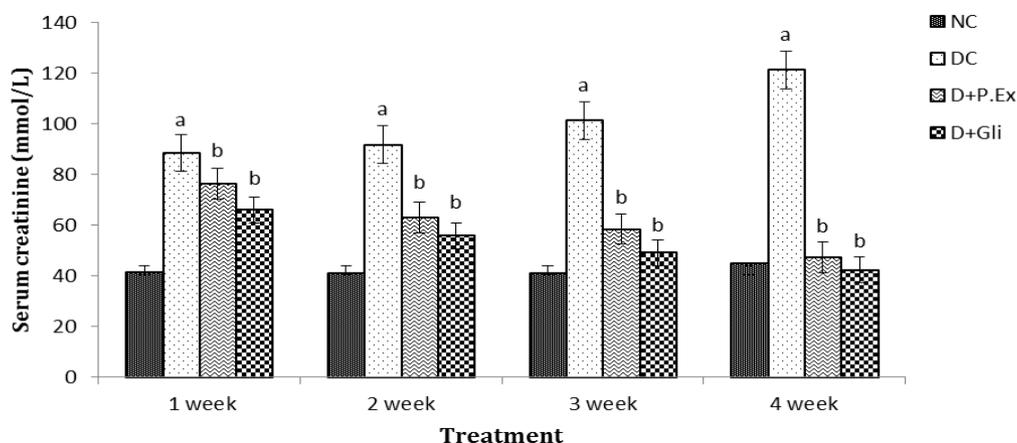
**Fig 7:** Effects of *Pimpinella tirupatiensis* extracts on serum ALP activity in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



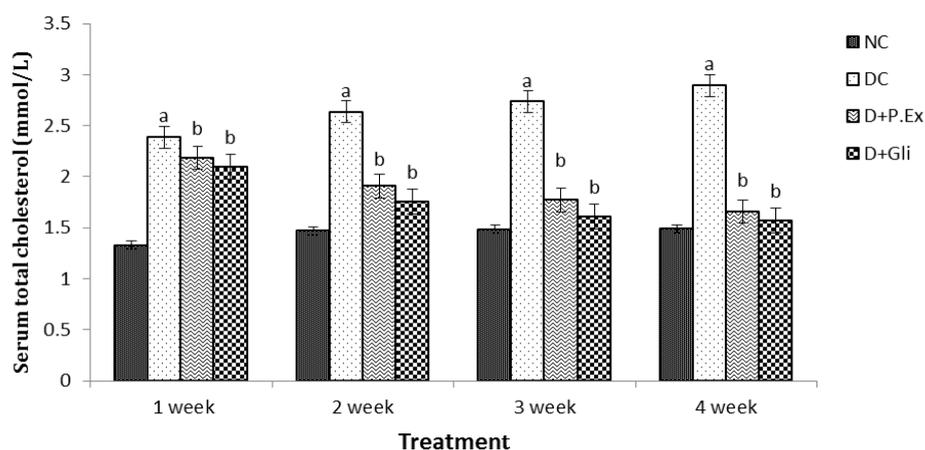
**Fig 8:** Effects of *Pimpinella tirupatiensis* extracts on serum urea level in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



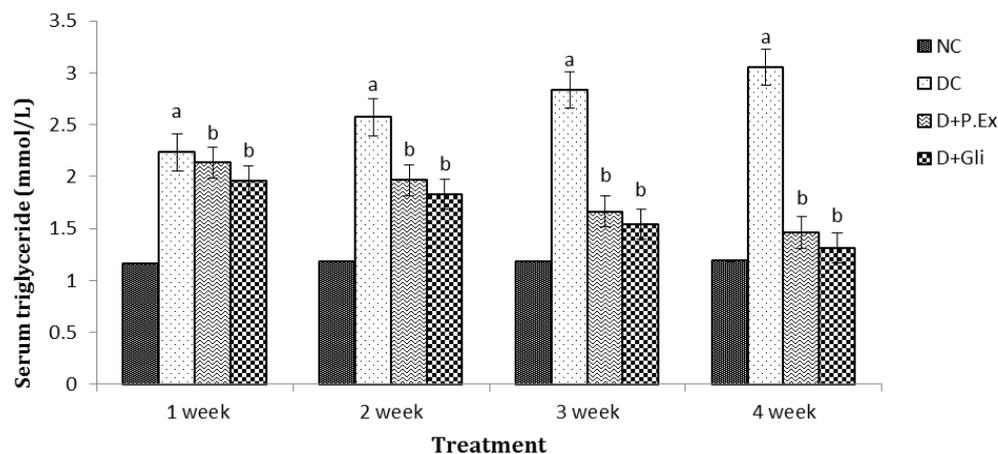
**Fig 9:** Effects of *Pimpinella tirupatiensis* extracts on serum creatinine level in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



**Fig 10:** Effects of *Pimpinella tirupatiensis* extracts on serum Total cholesterol in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



**Fig 11:** Effects of *Pimpinella tirupatiensis* extracts on serum triglyceride level in normal and streptozotocin-induced diabetic rats for 4 weeks of treatment. Each value is mean± SEM for six rats in each group. <sup>a</sup>  $p < 0.05$  by comparison with normal rats. <sup>b</sup>  $p < 0.05$  by comparison with streptozotocin diabetic rats.



## DISCUSSION

The increase in number of diabetic patients has motivated scientists to find safer and more effective antidiabetic drugs [4]. In spite of the presence of known antidiabetic medicines in the pharmaceutical market, therapies from herbal medicines are used with success for the management of diabetes [5]. The antidiabetic effects of these plants is due to their capability to restore the function of pancreatic  $\beta$ -cells by causing a rise in insulin production or by inhibiting the intestinal absorption of glucose or by the facilitation of metabolites in insulin dependent processes [9,11]. In this study investigated the antioxidant properties of *Pimpinella tirupatiensis* in streptozotocin- induced diabetic rats.

Streptozotocin- induced diabetic rats were characterized by a severe loss in body weight [1] and enhancement food and water intake [35] was observed showing similarity to polyphagia and polydipsia observed in human diabetics [2]. Body weight loss might be the result of protein wasting due to altered carbohydrate metabolism [7,14]. Treatment with *Pimpinella tirupatiensis* extract for a period of 4 weeks prevented the body weight loss and reduction of food and water intake in diabetic rats, which resulted from an improvement in glyceemic control.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) are considered as hepatic toxicity markers [26]. In streptozotocin - induced diabetic animals an alteration in the serum enzymes is directly related to the change in the metabolic mechanism of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) [10, 17]. Felig *et al.*, [12] reported that the augmented transaminases under insulin insufficiency were responsible for the amplified gluconeogenesis and ketogenesis during diabetes condition. Aspartate aminotransferase is an enzyme found mainly in the cells such as liver, heart, skeletal muscles, kidneys, and pancreas and in low amounts in red blood cells. It's serum concentration is proportional to the amount of cellular leakage, and is released into serum in larger quantities when any one of these tissue is leaked out or impaired, and it's rise is usually associated with cardiovascular disease or liver disease. Alanine aminotransferase is an enzyme found mainly in the liver and higher levels in serum induced liver damage [20]. The mechanism by which the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) are elevated in diabetic control may involve augmented liberation of these enzymes from tissues (mainly liver), owing to oxidative stress or the formation of progressive glycosylation end product [24]. Treatment of diabetic rats with *Pimpinella tirupatiensis* extract significantly decreased the activity of these enzymes as compared to untreated diabetic rats, indicated the preventing diabetic complications.

The kidneys eliminate metabolic wastes such as urea nitrogen, uric acid, creatinine and ions and thus optimum chemical composition of body fluids is maintained [31]. Hyperglycemia causes renal dysfunction such as acute glomerulonephritis, nephrosclerosis and even tubular necrosis by elevating serum urea nitrogen and creatinine [6,16,32]. In the present study, there was an elevation in serum urea nitrogen and creatinine in the streptozotocin- induced diabetic animals indicating the formation of renal hypertrophy, glomerular injury and renal dysfunction may be improved by the oral administration of *Pimpinella tirupatiensis* extracts supplementation.

Diabetes mellitus is usually associated with profound alterations in lipid metabolism, which is a metabolic disorder in diabetic complications [21,23]. Hyperglycaemia produced high levels of serum lipid profiles such as triglycerides and total cholesterol [29]. This hyperlipidemia associated with diabetes may be attributed to insulin insufficiency. In Normal conditions, insulin activates lipoprotein lipase, which hydrolyzes triglycerides. Insulin absence results in the deactivation of the enzymes, thereby causing hypertriglyceridemia [30]. Normalization of the blood glucose levels resulted in significant diminutions in serum lipid profiles and protein [18]. In the present study elevated serum lipid profiles such as (triglycerides, and total cholesterol,) were observed in diabetic condition. *Pimpinella tirupatiensis* treatment resulted in normalization of serum lipids profiles, which may contribute to the beneficial effect on pancreatic  $\beta$ -cells.

In summary for the first time we reported the effect of *Pimpinella tirupatiensis* extract on glucose homeostasis and metabolic parameters in experimental diabetic rats. Our results demonstrated that *Pimpinella tirupatiensis* extract are capable to protect diabetic- associated complication in streptozotocin-induced diabetic rats, which might be due to the stimulation of  $\beta$ -cells to secrete insulin. In addition, the capacity of the extract to decreased, lipid profiles and markers of renal dysfunction may contribute to its beneficial effects *in vivo*. Considering all these evidences, it is reasonable to undertake further studies on possible usefulness of extract of *Pimpinella tirupatiensis* in the management of diabetes mellitus.

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