

Original Research Article

Antihyperglycemic effect of an important phytochemical - Phloretin on Streptozotocin induced diabetes: An experimental study"

ABSTRACT

Aim: To investigate the antihyperglycemic effect of phloretin on streptozotocin induced diabetic rats. **Materials and Methods:** Diabetes mellitus was induced in adult male albino rats of Wistar strain weight ranges between 180-200g by intraperitoneal administration of streptozotocin (STZ) (60mg/kg b.w). Phloretin was administered orally to diabetic rats at two different doses like 25 and 50mg/kg b.w. The antidiabetic potential of phloretin was evaluated by analyzing the changes in body weight, blood glucose, total hemoglobin, glycosylated hemoglobin, insulin, liver glycogen and carbohydrate metabolizing enzymes like hexokinase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase and fructose-1, 6-bisphosphatase in the experimental rats. **Results:** Diabetic rats showed increased level of glucose and glycosylated hemoglobin and decreased level of body weight, serum insulin, hemoglobin and liver glycogen. **Increased activities** of gluconeogenic enzymes such as glucose-6-phosphatase and fructose-1, 6-bisphosphatase and **decreased activities** of hexokinase and glucose-6-phosphate dehydrogenase were observed in diabetic rats. The phloretin treated diabetic rats showed significantly reduced level of blood glucose and glycosylated hemoglobin and significantly increased level of body weight, serum insulin and liver glycogen. The altered activities of key enzymes of carbohydrate metabolism were significantly reverted to near normal in phloretin administered diabetic rats. **Conclusion:** The present findings suggest that phloretin may be useful in the treatment of diabetes mellitus and confirmed its antihyperglycemic effect mediated through the regulation of carbohydrate metabolic enzyme activities.

Keywords: Phloretin; streptozotocin; insulin; diabetes mellitus; antihyperglycemic effect

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disease with the highest rate of prevalence and mortality worldwide that is caused by an absolute or relative lack of insulin and/or reduced insulin activity, which results in hyperglycemia and abnormalities in carbohydrate, protein and fat metabolism[1,2]. It can be associated with serious complications and premature death, but people with diabetes should take steps to control the disease and lower the risk of complications [3], in spite of the use of many oral hypoglycemic agents such as sulphonylureas and biguanides. All of these pharmacological modalities also show limited efficacy and certain adverse effects such as liver toxicity, lactic acidosis, **diarrhoea** and attenuation of response after prolonged use and are expensive particularly for developing

countries like India and China [4]. Due to the side effects of antihyperglycemic agents for the treatment of diabetes, currently there is growing interest on plants and plant derived products [5]. The World Health Organization expert committee is also considering complementary and alternative approaches, including the use of herbal medicine with antidiabetic properties due to their natural origin and less side effects [6].

Globally prevalence of diabetes mellitus is an upward trend. The International Diabetes Foundation estimates that 366 million adults aged 20-79 were affected by diabetes worldwide in 2011 and this figure is expected to rise 552 million by the year 2030, with most of the increase coming from developing countries [7]. Liver is one of the chief storage organs for glucose reserve in the body and plays a crucial role in blood glucose homeostasis. It has been reported that the diabetic condition decrease the activities of enzymes in the glycolytic and pentose phosphate pathways, while increasing the activities of gluconeogenic and glycogenolytic pathways [8]. Liver cells have been used as an *in vitro* model for evaluating or screening the antihyperglycemic effect of plant or its constituents [9].

Medicinal plant based drug discovery continues to provide new and important leads against various pharmacological targets including diabetes [10]. A number of medicinal plants traditionally used in various herbal preparations for the management of diabetes and only a few of them have been proven scientifically [11, 12]. A few pharmaceutical trials are used to develop new biological agents derived from plants proved to be effective in the treatment of hyperglycemic threat [13]. Due to defective insulin secretion during diabetic condition, liver gluconeogenesis contributes to the elevation of blood glucose [14]. Numerous medicinal plants and their products have been proved to modulate the carbohydrate metabolic enzymes thereby help in maintaining the glucose homeostasis [15, 16,17].

Flavonoids are currently considered as promising natural substances to develop the modern therapy options against diabetes [18]. These groups of plant secondary metabolite nutraceuticals are well known for broad spectrum biological activities including antihyperglycemic effect. A few experimental evidences have demonstrated that the hypoglycemic effect of flavonoids are either through regulation of enzymes involved in carbohydrate metabolism or by stimulation of peripheral tissues for glucose uptake [19, 20].

Among the natural products, phloretin compounds are attracting much interest because of their beneficial effects. Phloretin, a natural active compound, belongs to flavonoids, exists in sap of apple, pear and other fruits and vegetables. Phloretin has been studied as a possible penetration enhancer for skin-based drug delivery [21], attenuates inflammation by antagonizing prostaglandins [22] and protects the skin from UV light-induced photodamage [23]. It can serve the purposes of antioxidation, antitumor, antibiosis and parahormone under physiological context [24, 25,26]. Phloretin is one of the antimutagenic factors that can be used for hepatoma treatment and other tumors, and thus it is a potential chemotherapeutic agent. There are 4 hydroxyl groups (-OH) in its chemical structure, which can inhibit the trans-membrane transport of saccharides leading to apoptosis of malignant cells [27].

There are many pharmacological studies using phloretin, but there is no study on the antidiabetic activity of phloretin. So, the present study was designed to evaluate the antihyperglycemic activity of phloretin by the analysis of biochemical parameters and the activities of carbohydrate metabolic enzymes in streptozotocin (STZ) induced diabetic rats.

2. MATERIALS AND METHODS

2.1 Chemicals

Phloretin (2',4',6'-trihydroxy-3-(p-hydroxyphenyl)-propiophenone; purity>98%) and Streptozotocin were purchased from Sigma Chemicals Company, St. Louis, Mo. USA. All other chemicals and reagents were of analytical grade and purchased from Himedia Laboratories Pvt. Ltd, Mumbai, India.

2.2 Animals

Male albino rats (*Rattus norvegicus*) weight ranges between 180-200g were used in the present investigation. The animals were housed in standard polypropylene cages and maintained under controlled room temperature and humidity with 12-h light and 12-h dark cycle. During the experimental period, the animals were fed with a diet of commercially available standard laboratory pellets purchased from Hindustan Lever Ltd, Bangalore and provided free access of water *ad libitum*.

2.3 Induction of Diabetes mellitus

Diabetes mellitus was induced in overnight fasted experimental rats by a single intraperitoneal injection of STZ (60mg/kg b.w) dissolved in freshly prepared citrate buffer (0.1 M, pH 4.5). After five days, the blood glucose was analyzed and determined the rats with fasting blood glucose greater than 250mg/dl were used in the present study.

2.4 Experimental Design

The total numbers of 30 rats were randomly divided into five groups of six rats in each group (24 diabetic surviving and 6 normal).

Group I: Normal control

Group II: Diabetic control

Group III: Diabetic rats treated with phloretin (25 mg/kg b.w.)

Group IV: Diabetic rats treated with phloretin (50 mg/kg b.w.)

Group V: Diabetic rats treated with glibenclamide (600µg/kg b.w.)

Two different doses of phloretin such as 25mg and 50mg/kg b.w were fixed for this study based on the previous report on chemopreventive role of phloretin against oral cancer [28]. Phloretin and glibenclamide were given orally to diabetic rats for 45 days daily at 10.00 a.m using intragastric tube. No death of the diabetic rats was observed till the end of study. The initial and final body weight of rats in each group was recorded. At the end of experimental period, the rats were deprived of food overnight and sacrificed by cervical decapitation. Blood was collected and the serum was separated for the estimation of glucose and insulin. Liver was dissected out, washed in ice-cold saline patted dry and weighed. The liver homogenate was used for biochemical investigations.

2.5 Biochemical Analysis

Serum glucose was estimated using a commercial kit (Sigma Diagnostics Pvt. Ltd., Baroda, India) by the method of Trinder [29]. Serum insulin was assayed by ELISA kit (Boehringer-Mannheim Kit, Mannheim, Germany) [30]. Hemoglobin and glycated hemoglobin were estimated by diagnostic kit (AgappeDiagnostic Pvt. Ltd., India) [31]. The estimation of protein was carried out by the method of Lowry et al. [32]. Glycogen content was assayed by the method of Ong and Khoo [33]. For this experiment, the liver samples were homogenised

119 with 10 volumes of ice-cold 30% KOH while frozen and boiled at 100° C for 30 min.
120 Glycogen was precipitated with ethanol, washed and resolubilized in water and then the
121 glycogen content was determined by treated with anthrone reagent. The green colour
122 developed was read at 625 nm.

123

124 A portion of the liver tissue was dissected out, washed with ice-cold saline and homogenized
125 with 0.1 M Tris-HCl buffer (pH 7.4) for the assay of key enzymes of carbohydrate
126 metabolism. The homogenate was centrifuged at 2000 g for 5 min to remove the debris and
127 the supernatant was used for the evaluation of enzymes of carbohydrate metabolism.

128

129

130 **2.5.1 Assay of Hexokinase**

131 Hexokinase was assayed by the method of Brandstrup et al. [34]. In this method, the
132 incubation mixture was prepared and it contained 1.0 ml of glucose, 0.5 ml of ATP solution,
133 0.1 ml of MgCl₂, 0.4 ml of K₂HPO₄, 0.4 ml of KCl, 0.1 ml of NaF and 2.5 ml of buffer. This
134 was preincubated at 37°C for 5 min and then the reaction was initiated by the addition of 0.5
135 ml of tissue homogenate. 1.0 ml of the reaction mixture was immediately transferred to a
136 tube containing 1.0 ml of TCA (control). A second aliquot was removed and deproteinised
137 after 30 min of incubation at 37° C. The protein precipitate was removed by centrifugation
138 and the residual glucose in supernatant was estimated in all the tubes by the method of
139 Trinder [29]. The enzyme activity was expressed as µmol of glucose
140 phosphorylated/hour/mg protein.

141 **2.5.2 Assay of Glucose-6-Phosphate Dehydrogenase**

142 Glucose- 6-phosphate dehydrogenase was measured by the method of Ells and Kirkman
143 [35]. In this method, the incubation mixture was prepared and it contained 1ml of Tris-HCl
144 buffer (0.05 M, pH 7.5), 0.1 ml of magnesium chloride, 0.1 ml of NADP⁺, 0.5 ml of
145 phenazinemethosulphate, 0.4 ml of 2,6-dichlorophenol indo phenol dye solution and 0.5 ml
146 of liver homogenate. The contents were incubated at 37° C for 10 min. The reaction was
147 initiated by the addition of 0.5 ml of glucose- 6-phosphate. The absorbance was read at 640
148 nm against water blank at 1 min intervals for 3-5 min using spectrophotometer.

149 **2.5.3 Assay of Glucose-6-Phosphatase**

150 Glucose-6-phosphatase was assayed by the method of Koide and Oda [36]. In this method,
151 the reaction mixture contained 0.7 ml of citrate buffer (0.1 M, pH 6.5), 0.3 ml of substrate
152 (0.01 M) and 0.3 ml of tissue homogenate and it was incubated at 37°C for 1 h. The reaction
153 of the enzyme was terminated by the addition of 1 ml of 10% trichloroethanoicacid. The
154 suspension was centrifuged and the phosphorus content of the supernatant was estimated
155 by the method of Fiske and Subbarow [37]. The supernatant was made up to known volume.
156 To this, 1 ml of ammonium molybdate followed by 0.4 ml of amino naphtholsulphonic acid
157 was added. The blue color developed after 20 min was read at 680 nm.

158

159 **2.5.4 Assay of Fructose-1, 6-bisphosphatase**

160 Fructose-1, 6-bisphosphatase activity was measured by Gancedo and Gancedo [38]. 2 ml of
161 assay mixture contained 1.2 ml of Tris-HCl buffer (0.1 M, pH 7.0), 0.1 ml of substrate (0.05
162 M), 0.25 ml of magnesium chloride (0.1 M), 0.1 ml of potassium chloride (0.1 M), 0.25 ml of
163 ethylene diaminetetraacetic acid (0.001 M) solution and 0.1 ml of enzyme homogenate. The
164 assay mixture was incubated at 37°C for 5 min. The reaction was terminated by the addition
165 of 1 ml of 10% trichloroethanoic acid. The suspension was centrifuged and then the
166 supernatant was used for phosphorus estimation by the method of Fiske and Subbarow [37].
167 The supernatant was made up to known volume. To this, 1 ml of ammonium molybdate was
168 added followed by 0.4 ml of aminonaphtholsulphonic acid. The blue color developed after 20
169 min was read at 680 nm.

170

171 2.6 Statistical Analysis

172 The results were expressed as mean $\pm$ S.D of six samples from each group (n=6). The
173 statistical significance was evaluated by one way Analysis of Variance (ANOVA) and the
174 individual comparisons were obtained by Duncan's Multiple Range Test (DMRT).

175

176 3. RESULTS

177

178 During the experimental period, the changes in body weight of normal and experimental rats
179 were measured and the results are represented in Table 1. The body weight was
180 significantly decreased ($P<0.05$) in diabetic rats when compared with normal control rats.
181 But, the body weight was significantly increased ($P<0.05$) in diabetic rats treated with
182 phloretin (25mg and 50 mg/kg b.w) and glibenclamide(600 μ g/kg b.w.) when compared with
183 diabetic rats.

184

185 The levels of blood glucose, total hemoglobin (Hb), glycated hemoglobin (HbA1c), insulin
186 and liver glycogen in normal and experimental animals were determined and the values are
187 depicted in Table 2. The diabetic rats showed significant increase ($P<0.05$) in the levels of
188 glucose and glycated hemoglobin and significant decrease ($P<0.05$) in the levels of total
189 hemoglobin, insulin and liver glycogen when compared with normal control rats. The levels
190 of blood glucose, total hemoglobin, glycated hemoglobin, insulin and liver glycogen were
191 extensively reversed by the administration of phloretin at the dose of 50mg/kg b.w as like as
192 the standard drug glibenclamide(600 μ g/kg b.w) treated diabetic rats.

193

194 Table 3 showed that the changes in the activities of hexokinase and glucose-6-phosphate
195 dehydrogenase in the liver of normal control and experimental rats. The hexokinase and
196 glucose-6-phosphate dehydrogenase activities were significantly decreased ($P<0.05$) in
197 diabetic rats when compared with normal control rats. Oral administration of phloretin at two
198 different doses like 25 and 50 mg/kg b.w to diabetic rats were significantly increased
199 ($P<0.05$) the activities of hexokinase and glucose-6-phosphate dehydrogenase as like as
200 glibenclamide treated diabetic rats.

201

202 Table 4 represented the activities of gluconeogenic enzymes like glucose-6-phosphatase
203 and fructose-1, 6-bisphosphatase in the liver of normal control and experimental rats. In this
204 study, the levels of glucose-6-phosphatase and fructose-1,6-bisphosphatase were
205 significantly increased ($P<0.05$) in diabetic rats when compared with normal control rats. Oral
206 administration of phloretin and the standard drug glibenclamide were significantly
207 decreased ($P<0.05$) the activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase
208 in liver of STZ-induced diabetic rats when compared with diabetic control rats.

209 **Table 1. Effect of phloretin on body weight**

Groups	Initial weight (g)	Final weight (g)	Change in body Weight (g)	Change in body weight (%)
Normal control	180±12.50	206±13.44 ^c	26±1.12 ^c	+14.44
Diabetic control	185±12.95	164±9.10 ^a	21±2.45 ^a	-11.35
Diabetic + Phloretin (25mg/kg b.w)	185±12.95	200±14.00 ^c	15±0.35 ^b	+8.10
Diabetic+Phloretin (50mg/kg b.w)	180±12.50	205±14.35 ^c	25±1.05 ^c	+13.88
Diabetic+Glibenclamide (600µg/kg b.w)	190±13.30	205±14.35 ^c	15±1.05 ^b	+7.89

210 *Values are expressed as mean ± SD of six rats from each group. Values are not sharing a common superscript letter differ*
 211 *significantly at 5% level (P<0.05) using Duncan's Multiple Range Test (DMRT).*

212 **Table 2. Effect of phloretin on blood glucose, total hemoglobin, glycosylated hemoglobin,**
 213 **insulin and liver glycogen**

Groups	Glucose (mg/dl)	Total hemoglobin (g/dl)	Glycosylated hemoglobin (mg/g Hb)	Insulin (µU/ml)	Glycogen (mg/g)
Normal control	85.23±5.96 ^b	14.54±1.15 ^c	3.24±0.19 ^c	53.21±1.98 ^c	56.46±3.94 ^c
Diabetic control	284±22.68 ^a	7.87±0.69 ^a	6.75±0.32 ^a	32.25±1.24 ^a	28.63±2.00 ^a
Diabetic+Phloretin (25mg/kg b.w)	98±20.06 ^b	13.80±1.10 ^b	3.85±0.21 ^b	45.57±1.35 ^b	42.76±2.98 ^b
Diabetic+Phloretin (50mg/kg b.w)	90±7.28 ^b	15.14±1.12 ^c	3.20±0.21 ^c	52.65±1.85 ^c	54.87±3.78 ^c
Diabetic+Glibenclamide (600µg/kg b.w)	97±20.77 ^b	14.81±1.03 ^{bc}	3.37±0.19 ^c	51.74±1.62 ^c	45.32±3.17 ^d

215 *Values are expressed as mean ± SD of six rats from each group. Values are not sharing a common superscript letter differ*
 216 *significantly at 5% level (P< 0.05) using Duncan's Multiple Range Test (DMRT)*

217 **Table 3. Effect of phloretin on the activities of hexokinase and glucose-6-phosphate**
 218 **dehydrogenase in the liver**

Groups	Hexokinase (μ moles of glucose phosphorylated/h/mg protein)	Glucose-6-phosphate dehydrogenase (μ moles of NADPH formed/min/mg protein)
Normal control	0.30 $\pm$ 0.04 ^c	5.28 $\pm$ 0.06 ^c
Diabetic control	0.14 $\pm$ 0.01 ^a	3.05 $\pm$ 0.08 ^a
Diabetic + Phloretin (25mg/kg b.w)	0.20 $\pm$ 0.02 ^b	3.75 $\pm$ 0.05 ^b
Diabetic + Phloretin (50mg/kg b.w)	0.28 $\pm$ 0.04 ^c	5.18 $\pm$ 0.09 ^c
Diabetic+Glibenclamide (600 μ g/kg b.w)	0.27 $\pm$ 0.04 ^c	4.94 $\pm$ 0.07 ^d

219 *Values are expressed as mean $\pm$ SD of six rats from each group. Values are not sharing a common*
 220 *superscript letter differ significantly at 5% level ($P < 0.05$) using Duncan's Multiple Range Test (DMRT).*

221
 222 **Table 4 . Effect of phloretin on the activities of glucose-6-phosphatase and fructose-**
 223 **1, 6-bisphosphatase in the liver**

Groups	Glucose-6-phosphatase (μ moles of inorganic phosphate liberated/min/mg protein)	Fructose-1,6-bisphosphatase (μ moles of inorganic phosphate liberated/h/mg protein)
Normal control	10.38 $\pm$ 0.05 ^c	4.84 $\pm$ 0.03 ^c
Diabetic control	17.38 $\pm$ 0.08 ^a	7.85 $\pm$ 0.09 ^a
Diabetic+Phloretin (25mg/kg b.w)	14.71 $\pm$ 0.02 ^b	5.82 $\pm$ 0.15 ^c
Diabetic+Phloretin (50mg/kg b.w)	10.99 $\pm$ 0.05 ^c	4.88 $\pm$ 0.04 ^c
Diabetic+Glibenclamide (600 μ g/kg b.w)	11.10 $\pm$ 0.06 ^c	4.95 $\pm$ 0.04 ^d

224 *Values are expressed as mean $\pm$ SD of six rats from each group. Values are not sharing a common*
 225 *superscript letter differ significantly at 5% level ($P < 0.05$) using Duncan's Multiple Range Test (DMRT).*

227 4. DISCUSSION

228
 229 Diabetes mellitus is a serious illness with multiple complications and premature mortality,
 230 accounting for at least 10% of total health care expenditure in many countries [39]. Global
 231 postulates that three fourth of the world population cannot afford the products of allopathic
 232 medicine and thus they have to rely upon the use of traditional medicines are largely derived
 233 from plants [40]. Some substances have shown antidiabetic effect by influencing β - cell to
 234 stimulate insulin secretion and restore insulin sensitivity [41].

235
 236 In the present study, we observed that the loss of body weight and excess of food and water
 237 intake by STZ-induced diabetic rats than normal rats. These results coincide with earlier
 238 report [42]. The characteristic loss of body weight is mainly due to increased water

239 intake, polyuria, dehydration, muscle wasting, excessive hair loss and increased food intake
240 [43]. Hence, a notable gradual decrease in body weight might be the result of protein
241 wasting due to the unavailability of carbohydrates for energy metabolism and the loss or
242 degradation of structural proteins [44].

243

244 The non-enzymatic, irreversible covalent bonding of glucose with Hb in the circulation leads
245 to the formation of HbA1c, which is used to predict the diabetic risk of individuals [45]. About
246 16% increase of HbA1c in patients with diabetes mellitus and the amount of increase is
247 directly proportional to the fasting blood glucose level. In diabetes, the excess glucose
248 present in blood reacts with Hb and thus Hb level was decreased in diabetic rats. In the
249 present study, the level of HbA1c in diabetic rats was significantly increased when compared
250 to normal control rats. It indicates their poor glycemic control and this result is consistent with
251 other studies [46, 47]. Administration of phloretin prevents the formation of HbA1c and
252 increasing the level of Hb in diabetic rats. This may be due to the restoration of blood
253 glucose and reducing the intensity of Hb glycation.

254

255 Liver is mainly responsible for maintaining the normal level of blood glucose by its ability to
256 store glucose as glycogen and to produce glucose from glycogen breakdown or from
257 gluconeogenic precursors [48]. During the experimental period, the selective destruction of
258 pancreatic β -cells by streptozotocin leads to the decreased level of plasma insulin and it
259 cause the defective glucose oxidation and hyperglycemia. The fundamental mechanism
260 underlying hyperglycemia in diabetes mellitus involves over-production (excessive hepatic
261 glycogenolysis and gluconeogenesis) and decreased utilisation of glucose by the tissues
262 [49]. In the present study, the administration of phloretin to diabetic rats induced the insulin
263 secretion significantly and thus decreases the blood glucose level. Similarly, the oral
264 administration of phloretin to C57BL BKS-DB mice significantly decreased the blood glucose
265 and improved glucose tolerance was reported [50].

266

267 Glycogen deposition in peripheral tissues and liver occurs after meal is a physiological
268 response in mammals to maintain the blood glucose concentration [51]. Diabetes mellitus
269 impairs the normal capacity of the liver to synthesize glycogen and low content may be
270 attributed to lack of insulin. In this study, oral administration of phloretin significantly
271 increased the level of liver glycogen which indicates that the better insulin activity in diabetic
272 rats. These results are in agreement with the previous study, in that lowering of blood
273 glucose level was accompanied by increased level of liver glycogen after S-allylcysteine
274 supplementation to STZ induced diabetic rats [52].

275

276 Liver is an important organ that plays a vital role in glycolysis and gluconeogenesis.
277 Hexokinase is an insulin-dependent and an insulin-sensitive enzyme and it is almost
278 completely inhibited or inactivated in the liver of diabetic rats due to the absence of insulin
279 [53]. Hexokinase insufficiency in diabetic rats can cause decreased utilization of glucose for
280 energy production [54]. Similar results were obtained in the present study and thus the
281 administration of phloretin to diabetic rats showed significant reversal in the activity of
282 hexokinase. In this study, the increased level of serum insulin and decreased level of
283 glucose were observed in diabetic rats treated with phloretin. The diabetic rats treated with
284 phloretin showed increased hepatic hexokinase activity and thereby increased
285 glycolysis. These results are in agreement with the previous study, in that they reported that
286 the flavonoid compound esculetin improved hexokinase activity in STZ-induced diabetic rats
287 [55]. A decrease in the activity of glucose-6-phosphate dehydrogenase slows down the
288 pentose phosphate pathway in diabetic condition [56]. In this study, diabetic rats treated
289 with phloretin showed significantly increased liver glucose-6-phosphate dehydrogenase
290 activity through enhanced secretion of insulin.

291

Glucose-6-phosphatase plays a vital role in the homeostasis of blood glucose [57]. Fructose-1, 6-bisphosphatase is one of the key enzyme of the gluconeogenic pathway. In this study, the activities of gluconeogenic enzymes such as glucose-6-phosphatase and fructose-1, 6-bisphosphatase were increased significantly in the liver of diabetic rats. The activities of glucose-6-phosphatase and fructose-1, 6-bisphosphatase were significantly lowered in diabetic rats treated with phloretin which might be due to increased secretion of insulin. Similarly, the researchers reported that the flavonoid umbeliferone improves glucose metabolism in diabetic rats by the inhibition of gluconeogenesis [58].

4. CONCLUSION

The administration of phloretin to diabetic rats showed that the significant restoration of body weight, blood glucose, insulin, haemoglobin, glycated hemoglobin, liver glycogen and key enzymes of carbohydrate metabolism. So, the present study confirmed that the phloretin enhances the glycolytic enzymes and control the glucose metabolism in streptozotocin induced diabetic rats. Therefore from this study, we concluded that the phloretin might be an effective plant based antihyperglycemic agent in future.

ETHICAL APPROVAL

Authors have hereby declared that the principles of laboratory animal care were followed and all experiments have been examined and approved by the Institutional Animal Ethical Committee of Bharathidasan University, Tiruchirappalli-612 024, Tamilnadu, India as per the guidelines of CPCSEA, India.

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