Original Article

The Ameliorative Anti-Diabetic Effect of Berberin on Testis Histology of Male Albino Rat *Rattus norvigicus*

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Abstract

Background: Berberine is a supplement of an active compound that has been documented as a plant source with anti-diabetic activity, and its properties are related to its antioxidant activity. **Objective:** To evaluate the ameliorative and recovering effects of berberine against the reproductive diabetic complications. **Materials and Methods:** Thirty male rats were used in current study, divided randomly into five groups: first group rats were administered normal saline, second group were injected with streptozotocin 55 mg/kg of body weight, third group received 200 mg/kg berberine, and fourth and fifth groups were represented diabetic rats and given 200 mg/kg body weight of berberine for 45 and 90 days, respectively. Blood was withdrawn and organs were excluded after the sacrificing of animals. **Results:** Results explained a significant decrease ($P < 0.05$) in body weights of all treated groups compared to control. A significant increase in fasting blood glucose of diabetic animals compared with berberine and control groups, and a non-significant differences between the two diabetic groups treated with berberine compared with controls in fasting glucose and insulin levels were noted. Histopathology exhibited degeneration and necrosis in the germinal epithelium of the seminiferous tubules with congested blood vessels and hemorrhage in the interstitial tissue. Treatment with berberine was reduced the necrotic effects of diabetes and restored the cellular architecture of testis tissue according to the duration of administration. **Conclusion:** Berberine has an ameliorative effects on biochemical and histological parameters in diabetic animals.

Keywords: Berberine, diabetes, histology, rat, testis

Introduction

The World Health Organization documented more than 220 million worldwide spread of diabetes.[1,2] According to the International Diabetes Federation, the global prevalence of diabetes among people between the ages of 20 to 79 in 2021 was 10.5%, which is predicted to rise to 12.2% in 2045.[1,2] Diabetes, a metabolic disease, remarked as an increase in blood glucose levels as a result of one of the following causes: Beta cells destruction or increasing the insulin resistance. There are two types of diabetes; Type 1 (β-cell losing) and Type 2 (decrease the target tissue receptiveness or sensitivity toward insulin).[3-6] Many plants' extracts were used as anti-diabetics, as they have anti-diabetic activity, and they provide an imperative sources for the progression of diabetes treatments.[7] Berberine is a supplement of an active compound that has been documented as a plant source with anti-diabetic activity, and its properties are related to its antioxidant activity.[8-10] Berberine is an isoquinoline of alkaloid with proto-berberine structural class.[11] Several studies.[12,13] have shown that berberine has various properties being applied in the pharmaceutical trials such as anti-diabetic and antihyperlipidemic,[14] inflammatory,[15]and anticancer.[16]

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Materials and Methods

Induction of diabetes

Induction of diabetes was carried out through the intraperitoneal injection of a single dose of streptozotocin 60 mg/kg of animal rats body weight.[17,18] Fasting blood glucose (FBG) levels were measured weekly by the use of

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glucometer type and model rats with FBG > 200 mg/dL were referred as diabetic animals.

Experimental design

Thirty male adult healthy albino rats aged 2–3 months were used in the current study. They all were adapted and delivered with water and food. All experiments in this were carried out in accordance with the guidelines laid down by the International Animal Ethics Committee or Institutional ethics committee and in accordance with local laws and regulations. Diabetic and normal animals were divided randomly into five model groups as following: six rats as negative control group were received normal saline, six as diabetic rats, six rats as positive control for berberine supplement, and six diabetic rats were orally administered 200 mg/kg of body weight[19] for 45 and 90 days, respectively. Serum insulin levels were measured using rat insulin kit (Cusabio, Houston, Texas, USA). FBG levels were evaluated by the use of glucometer Glucometer (Roche, Basel, Switzerland).

Blood and organs sampling

Throughout the study period, blood was withdrawn by puncturing the caudal vein for measuring FBG using glucometer. After 1 week of last administration, heart puncturing was done for collecting blood for the measuring some biochemical parameters needed, and the testis were extruded, weighted, and fixed in formalin fixative for tissue processing.

Statistical analysis of data were done using SPSS software (IBM, New York, USA), using one-way ANOVA at significance level ($P < 0.05$), and expressed as mean ± Standard error.

Ethical approval

All experiments were carried out in accordance with the guidelines laid down by the International Animal Ethics Committee or Institutional ethics committee and in accordance with local laws and regulations, approved was obtained at August 17, 2022 with number 332.

Results

Results presented in Table 1 shows some changes of body weight in experimental animals. There was a significant decrease ($P < 0.05$) in the body weight of diabetic animal group compared to normal control and berberine animals, which showed an increased body weight. In diabetic group treated with berberine, there was a significant decrease ($P < 0.05$) in their body weights compared with the two control groups.

Results presented in Table 2 shows a significant increase in FBG in diabetic animal group compared with control group and berberine, whereas diabetic-treated animals with berberine exhibited a non-significant difference in FBG compared with control group. The result related to insulin levels exhibited that there was no significant differences between the two diabetic groups treated with berberine and control group.

Discussion

As mentioned above berberine has many pharmaceutical properties that could ameliorate and protect against many diseases.[20] Results shown in Tables 1 and 2 explain the abnormal glucose metabolism that is closely related

Table 1: The differences in body weight for control, diabetic, berberine, and diabetic treated with berberine rats

Groups/n = 6	Body weight/g (mean ± SE)		Weight difference %
	Initial	Final	
Control	230 ± 7.5	278 ± 7.1	48d
Diabetics	225 ± 10.4	191 ± 9.2	–34b
Berberine	270.5 ± 2.6	277 ± 5.4	6.5c
Diabetics **berberine/**45 days	320 ± 13.2	291 ± 11.9	–29a
Diabetics **berberine/**90 days	315 ± 5.2	289 ± 2.4	–26a

Different letters refer to the significant differences among animals groups ($P < 0.05$)

Table 2: The mean fasting blood glucose levels and serum insulin for control, diabetic, berberine, and diabetic treated with berberine rats

Group/n = 6	Fasting blood glucose (mg/dL)	Serum insulin (ng/dL)
	Mean ± SE	
Control	122 ± 2.9b	0.301 ± 1.1b
Diabetics	460 ± 22.7c	0.157 ± 0.07a
Berberine	98.4 ± 3.6a	0.187 ± 0.04a
Diabetics berberine/45 days	110 ± 4.1ab	0.395 ± 0.09c
Diabetics berberine/90 days	115 ± 2.8b	0.348 ± 0.4b

Different letters refer to the significant differences among animals groups ($P < 0.05$)

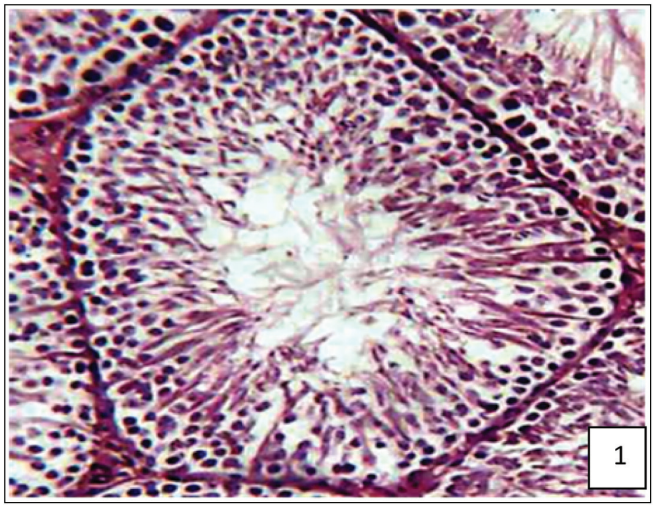

Figure 1: Cross section of testis from negative control group rat treated with normal saline explained the intact normal seminiferous tubule architecture (H&E stain 40×)

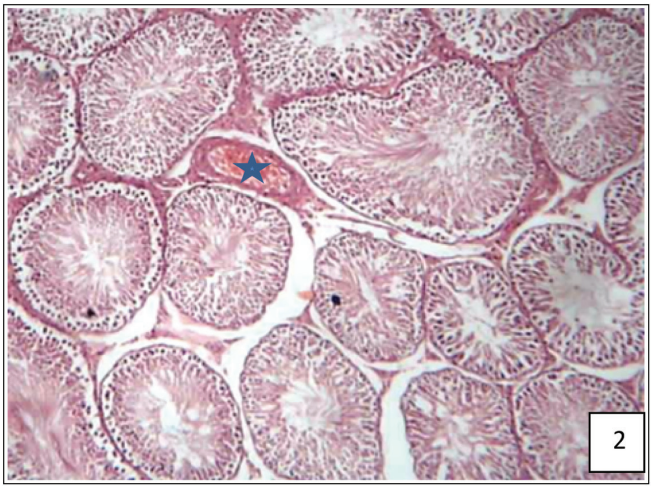

Figure 2: Cross section of rat testis from streptozotocine induced diabetes group exhibited the presence of hemorrhage (blue star) with widening between the seminiferous tubules with degeneration and defect and necrosis in spermatogenesis cells (black stars) (H&E stain 4×)

to the onset of diabetes by the use of streptozotocin[21] and it displayed the ameliorative effects of the berberine on bodies weight and biochemical parameters as a result of its anti-diabetic effect that was related to its property of lipid modulation and the stimulation of insulin secretion.[22,23] It was also showed that diabetic animals treated with berberine exhibited decreased glucose levels and increased insulin levels in their serum. Berberine improved insulin sensitivity, enhanced insulin release, and positively affected glucose and lipid metabolism. Additionally, it demonstrated antioxidant properties that countered oxidative free radicals associated with diabetes, while suppressing glucose uptake through enterocytes.[24-26] Also Qin *et al.*[27] explained that berberine could play an important role against the metabolic stress and could keep homeostasis.

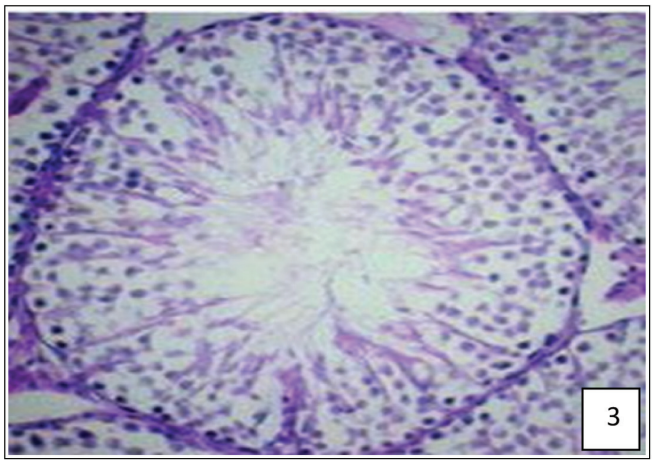

Figure 3: Cross section of testis from positive control group rat treated with berberine explained the intact normal seminiferous tubule architecture (H&E stain 40×)

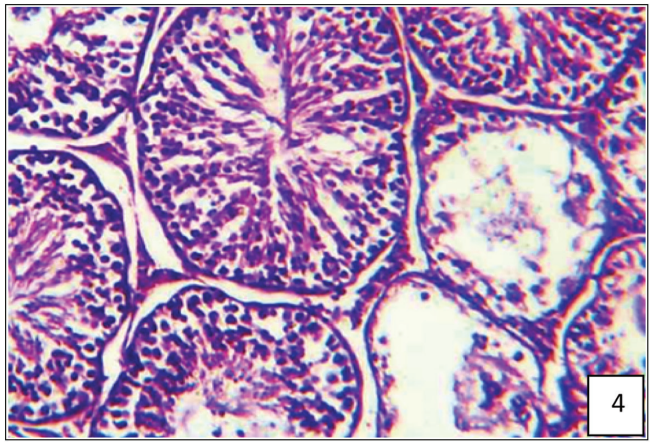

Figure 4: Cross section of rat testis from streptozotocine induced diabetes group treated with berberine for 45 days exhibited the improvement of the seminiferous tubules architecture with some necrosis (H&E stain 10×)

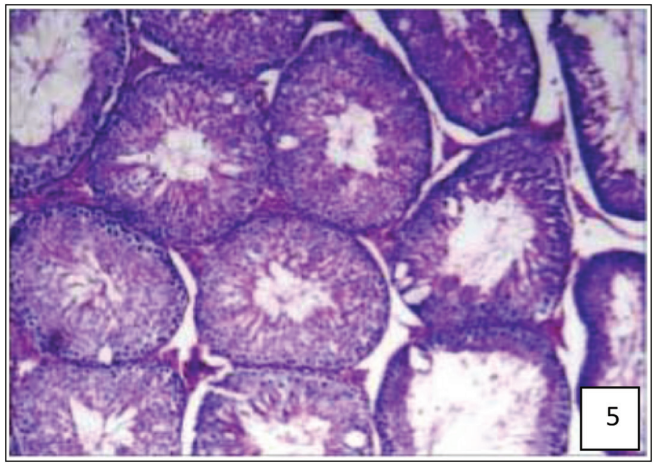

Figure 5: Cross section of rat testis from streptozotocine induced diabetes group treated with berberine for 90 days exhibited the improvement of the seminiferous tubules architecture (H&E stain 10×)

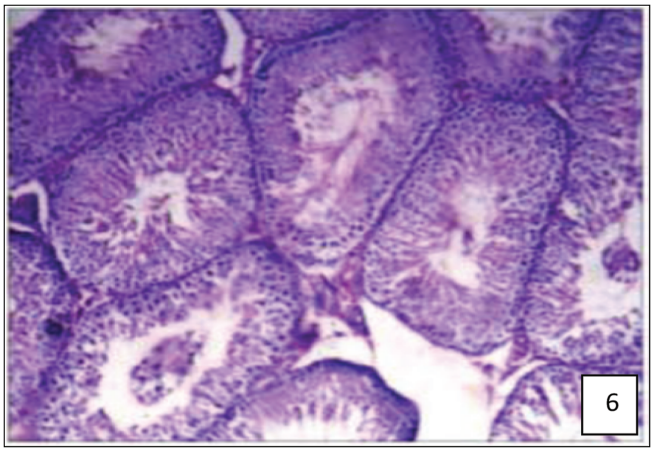

Figure 6: Cross section of rat testis from streptozotocine induced diabetes group treated with berberine for 90 days exhibited the improvement of the seminiferous tubules architecture (H&E stain 10×)

Hematoxylin and eosin microscopic examination explained that the induction of diabetes in rat of the present study resulted in the reduction of spermatogenic cells and it was associated with a degeneration in spermatogenic cells series with congestion in blood vessels of the interstitium connective tissue [Figures 1 and 2]. Diabetes was reported to decrease the count of the spermatogenic cells with reduction in seminiferous tubules diameters, and observations that could be documented as indicators for degenerated spermatogenesis as explained by Dkhil *et al.*[28] Also, those degenerative changes that resulted from diabetes were reported to be caused via the oxidative stress and apoptosis.[29]

Histological results [Figures 3-6] of the two testis cross sections from diabetic-berberine treated rats exhibited a semi-normal seminiferous architecture, an observation that agreed with the documentation of[30,31] who used berberine fraction containing plant extract and explained its antioxidant properties through the reduction of TBARS and NO levels with a decrease in levels of glutathione. So it is reported as the most potent antioxidant agent that could protect the organs cells against the destructive effects of the reactive oxygen species damages, as it could inhibit the phosphorylation of JAK2 tumor cells.[32] Also the results demonstrated that berberine was sufficient to repair the damaged testicular seminiferous tubules in long-term diabetes by reconstructing tight junctions and blood-testis barrier, a result that agreed with Gao *et al.*[33] and Zainal[34] and Shareef *et al*.[35] reported that berberine can inhibit the phosphorylation of JAK2 in tumor cells.

Conclusion

The present study was an insight into the adverse effects of diabetes on testicular seminiferous tubules and the ameliorating effect of berberine against those harm complications during time periods and it was found that long-term administration could restore the normal testicular architecture.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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