

## The Antidiabetic Activity of Curry Leaves “*Murraya Koenigii*” on the Glucose Levels, Kidneys, and Islets of Langerhans of Rats with Streptozotocin Induced Diabetes

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### Abstract

**Background:** The aims of this study were to explore the antihyperglycemic effect of curry leaves, *Murraya koenigii* “MK” aqueous extract, and to examine its possible protective effects on the islets of Langerhans and kidneys of streptozotocin (STZ) diabetic rats. **Methods:** Thirty healthy adult male Sprague Dawley rats were randomized into five groups (n=6); normal control, normal treated with “MK” control, diabetic control (non-treated with “MK”), diabetic treated with 200 mg/kg MK aqueous leaf extract and diabetic treated with 400 mg/kg MK aqueous leaf extract. Blood glucose levels and body weight were monitored gravimetrically. The animals were sacrificed on the 30th day; the kidney and pancreatic tissues were processed for histological studies. **Results:** The diabetic group showed considerable loss of body weight and increase in blood glucose levels and degeneration of the glomeruli and renal convoluted tubules and atrophied islets with disintegration of  $\beta$ -cells. Treatment of diabetic rats with MK extract showed significant ( $p < 0.001$ ) improvement in blood glucose levels and body weight gain. The MK extract also caused an improvement in tissue injury induced by STZ injection in the kidney and islets of Langerhans. **Conclusions:** These findings highlighted the beneficial effects of MK aqueous extract against cellular oxidative damage in STZ-induced diabetic rats.

**Keywords:** blood glucose, body weight, islet of langerhans, kidney

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### Introduction

Diabetes mellitus (DM), is the commonest metabolic disease, involves metabolic disorder of carbohydrates, proteins and lipids is often characterized by “chronic hyperglycemia”, and is currently considered as one of the five leading causes of death worldwide; it has become a serious problem threatening the global public health in view of its associated fatal vascular complications and the lack of effective long term treatment.<sup>1</sup> The prevalence of diabetes is rising globally both in developed and developing countries and it has become an important health concern and the leading cause of chronic renal failure in Brazil, The South Asian region, and The United Kingdom.<sup>2-4</sup>

Diabetic nephropathy is a spectrum of progressive renal lesions secondary to DM ranging from renal hyperfiltration to end stage kidney disease; it is associated with a state of decreased total protein concentration and increased urea level.<sup>5</sup> Glomerular lesions mimic to those found in human diabetes have been observed in experimental animals treated with streptozotocin (STZ).<sup>6</sup>

STZ has a high specific cytotoxic action on the  $\beta$  cells of the pancreatic islets and has been shown to induce a chronic diabetic state in animal’s model.<sup>7,8</sup> Induced DM by STZ in many animal species has been reported to resemble human hyperglycemic DM as it develops many features as seen in human patients.<sup>9</sup> Long-term effects of STZ induced diabetes in experimental animals demonstrated glomerular nephropathy along with tubular degeneration, and massive inflammatory infiltrates in the interstitial tissue.<sup>6,10</sup>

Currently many medicinal plants have been recommended for the treatment of diabetes.<sup>11,12</sup> Curry leaves, *Murraya koenigii* (MK), are natural flavouring agents with a number of important health benefits that makes food healthy and enhances both taste and aroma. They are rich in medicinal nutraceutical properties and even have cosmetic uses.<sup>13</sup> The major phytoconstituents identified in MK are carbazole alkaloids, glycosides, and flavonoids.<sup>14</sup> The antihyperglycaemic effects of MK in different animal models have been reported in many literatures with variable results. Significant blood glucose lowering effects of dose dependent MK aqueous extract has been

reported in both diabetic rabbits and rats.<sup>15-17</sup> The objectives of this study were to investigate the effects of the aqueous crude extract of MK on serum glucose levels and histopathological changes in the kidney and the islets of Langerhans in STZ induced diabetes mellitus in rats.

## Methods

**Plant Material.** Fresh plant material was obtained from the local wet market in Kuantan, Pahang, Malaysia. Specimen sample was authenticated by a Taxonomist and deposited in the Faculty's Herbarium. Isolated fresh leaves were dried and pulverized to powdered using the Fritsch universal cutting mill (AZM-160-23) and stored in a desiccator at 20 °C for subsequent use in the experiment.

**Preparation of aqueous extract.** The powdered leaves (600 g) were subjected to cold maceration in 2 L of distilled water on three occasions, with intermittent stirring at 48 hour intervals. The extract was filtered and the yield was 550 mL. The extract was concentrated using a rotary vacuum evaporator (BUCHI R-205) to a final adjusted volume of 500 mL. The concentrated water soluble extract (500 mL) was frozen at – 70 °C and were immediately freeze dried for a continuous two week period until the extract was completely dried, with the final extract weighing 78 g. The extract was then preserved in the laboratory chiller at 2 °C for subsequent use. The final concentration of the aqueous extract was adjusted to 100 mg/mL.

**Animals and experimental design.** Thirty healthy adult male Sprague Dawley rats (12 normal; 18 diabetic) of 10-12 weeks old and body weight 150-250 g were housed (in triplets) in polypropylene cages under standard laboratory conditions (temperature: 24 ± 4 °C; relative humidity: 46-79%; 12:12 hrs light: dark cycle, adequate cross ventilation) and were allowed one week period to acclimatize prior to the test. The rats were divided into five groups of six animals each, they were fasted overnight and their fasting blood sugar (mmol/L) was measured. The first group (NC1/normal control rats). The second group (NC2/normal treated control rats) was given MK 400 mg/kg; the third group (DC/diabetic control rats) was given 70 mg/kg STZ; the fourth group (MK-200/diabetic rats treated with curry leaf 200 mg/kg MK) was given 70 mg/kg STZ and 200 mg/kg MK, the fifth group (MK-400/diabetic rats treated with curry leaf 400 mg/kg MK) was given 70 mg/kg STZ and 400 mg/kg MK. All groups were maintained on standard commercial dry pellet diet containing 22% crude protein, 46% fat, 4% fibre, 7.6% ash, 12.0% moisture, 1.2% calcium, and 0.73% phosphorus (Gold Coin Feed Mills Sdn. Bhd. Kuala Lumpur, Malaysia), and water *ad libitum* (Table 1).

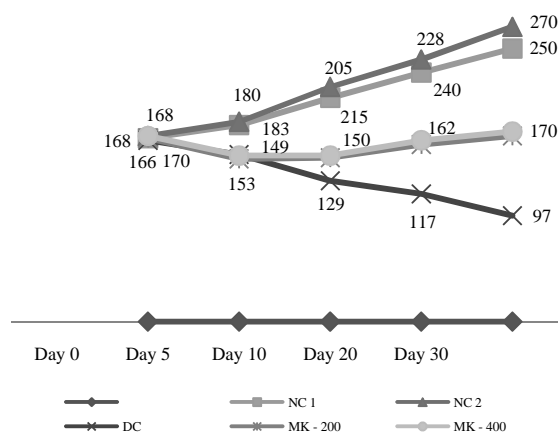
Diabetes was induced under light ether anesthesia by a single intraperitoneal injection of 70 mg/kg of STZ. The

**Table 1. Distribution of Rats into Groups According to the Treatment**

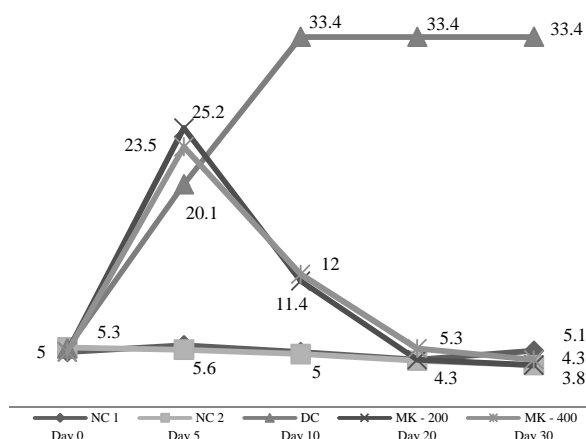
Group	Definition	Treatment
NC 1	Normal control rats	Rat pellets and water only
NC 2	Normal treated control rats	Rat pellets, water & MK 400 mg/kg
DC	Diabetic control rats	STZ 70 mg/kg, + pellets and water
MK-200 mg/kg/day	Diabetic rats treated with curry leaf (MK) 200 mg/kg	STZ 70 mg/kg, MK - 200 mg/kg + pellets and water
MK-400 mg/kg/day	Diabetic rats treated with curry leaf (MK) 400 mg/kg	STZ 70 mg/kg, MK - 400 mg/kg + pellets and water

injected volume was prepared to contain 1.0 mL/kg. Rats were supplied with 5% glucose solution for 48hrs immediately after STZ injection to counteract severe acute hypoglycemic effect. Control rats received an equivalent volume of phosphate buffered saline. Diabetes induction was confirmed by determination of high fasting blood glucose (FBG) level, on the fifth day after STZ administration. Rats with FBG level ≥ 14 mmol/L were selected for subsequent experiment. Following the confirmation of diabetes, oral treatment with MK aqueous extract using oral gavage was started on the sixth day after STZ administration and it was considered as the first day of treatment. Oral gavage was performed with the aid of special designed metal ball-ended needle and syringe. FBG levels and body weight (g) measurements for all rats were recorded on day 3, 10, 20, and 30 of the experiment. Blood samples from the overnight fasted normal and STZ-induced diabetic rats were obtained from the rat tail vein after a mild prick for repeated measurement of FBG by glucometer (Life Scan One-touch Ultra Glucose Meter, USA) on day 0, 5, 10, and 20 of the experiment. On the 30th day animals were sacrificed using high dose Nembutal anesthesia. Pancreatic and renal samples from each group of rats were fixed in 10% formal saline for 72 h, dehydrated by ethanol, cleared in xylene and embedded in paraffin wax. Sections of 5 µm thickness were stained with Hematoxylin and Eosin (H & E). Images that showed considerable histological differences from control group were captured and studied by two experienced pathologists who were blind to study groups. The animals were treated according to the standards and regulations for the Care and Use of Laboratory Animals of the National Institutes of the Health and to the guidelines of IIUM animal ethical committee number (IIUM/519/14/ 4/IACUC).

**Statistical Analysis.** Results were expressed as mean ± SD. Comparison of the mean values between the respective groups at various time intervals was done using one-way repeated measure analysis of variance (ANOVA), followed by Tukey's honestly significant difference (HSD) test.  $p < 0.05$  were considered statistically significant.



**Figure 1. Effect of MK Aqueous' Extract on Body Weight (g) at Various Time Intervals in Normal and STZ-induced Diabetic Rats**



**Figure 2. Effect of MK Aqueous' Extract on Fasting Blood Glucose Levels (mmol/L) at Various Time Intervals in Normal and STZ-Induced Diabetic Rats**

## Results

**Effect of MK aqueous extract on body weight.** The mean basal body weight values for all the animal groups ranged from 166 to 172 grams with no significant inter-group variation. Five days after STZ administration the diabetic rat (DC) groups showed insignificant marginal loss of body weight in comparison to the normal control (NC 1) and showed continuous decrease throughout the experimental period with maximal reduction of 42% ( $p < 0.001$ ) achieved on 30<sup>th</sup> day in comparison to the basal level. In contrast, the normal control rats (NC 1), achieved 55% increase in body weight at the end of the experiment.

Regaining of body weight among the treated groups (MK 200 and MK 400) started marginally from the 10<sup>th</sup> day, stabilized around the 20<sup>th</sup> day and equilibrates basal levels by the 30<sup>th</sup> day of the experiment (Figure 1). However, these groups still maintain statistically significant difference ( $p < 0.001$ ) in comparison to the normal rats weight gain at the same corresponding time intervals. The overall result as depicted in Figure 1, shows statistically significant difference for day in all the five groups (Wilk's Lambda = 0.018,  $F(5, 26) = 275.9$ ;  $p < 0.001$ , eta squared = 0.982 and observed power = 1.00).

### Antihyperglycemic effect of MK aqueous extract.

The basal mean FBG levels for all groups of rats were not statistically different from each other ( $M = 5.0$ ,  $SD = 0.7$ ,  $p > 0.05$ ). However, on the fifth day after STZ administration the values advanced three to five folds higher ( $p < 0.001$ ) in all other groups (DC, MK 200 and MK400) when compared to normal controls (NC1) group. Blood glucose levels in all the treated groups (MK 200 and MK 400) at various time intervals decreased marginally towards normal value, unlike in the diabetic control (DC) group where it remained persistently high. However, the percentage of blood glucose reduction was not dose dependent among the MK treated groups (MK 200 and MK 400); for example, maximal reduction achieved by MK 200 mg/kg (85%) on 30<sup>th</sup> day was slightly above than that of MK 400 mg/kg (83%) on same day. The mean fasting blood sugar level for diabetic control (DC) group ( $M = 34.01$ ,  $SD = 3.33$ ) remained statistically significant ( $p < 0.001$ ) in comparison to the treatment groups throughout the experimental period. On the other hand, the normal control groups (ideal "NC1" and "NC2" treated) showed persistent normoglycaemic values throughout the course of the study. The overall result (Figure 2) shows statistically significant difference in all the five groups (Wilk's Lambda = 0.018,  $F(5, 26) = 275.9$ ;  $p < 0.001$ , eta squared = 0.982 and observed power = 1.00).

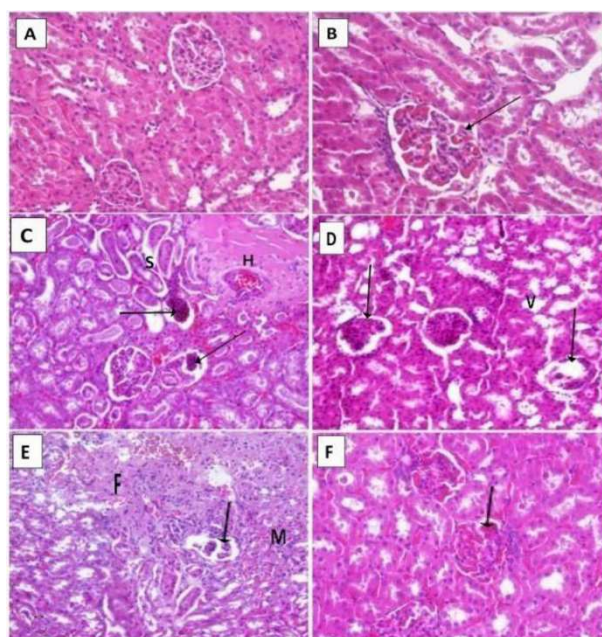
**Histological observation.** The kidneys of rats of both control groups (NC1 and NC2) showed normal histological structure; the renal cortex consisted of numerous renal corpuscles, which were formed of tuft of capillaries "glomerulus", enclosed by Bowman's capsule. Both proximal and distal convoluted tubules were normal (Figure 3A).

The kidneys of the STZ hyperglycaemic rats showed variable pathological changes in glomeruli and renal convoluted tubules; there was a moderate enlargement of glomeruli, dilatation and congestion of glomerular capillaries in comparison to the control group (Figure 3B). The proximal convoluted tubules were filled with a heterogeneous eosinophilic material, and haemorrhage was also seen in the Bowman's space that was related to the glomerular damage (Figure 3C). Some sections

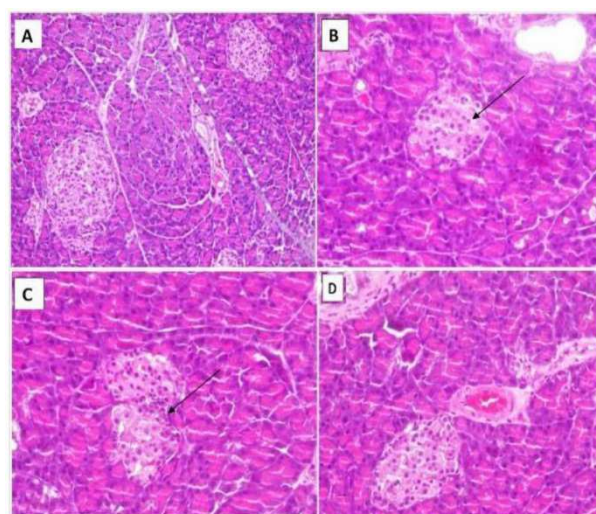


exhibited degeneration of the glomeruli as end stage associated with mesangial cells hyperplasia, hydropic tubular epithelium, vacuolations and dilatation (Figure 3D). Some sections in few rats showed the presence of interstitial fibrosis associated with destroyed glomeruli and mononuclear inflammatory cells infiltration (Figure 3E). The incidence and intensity of glomerular degeneration and tubular vacuolations were much lower in STZ-diabetic rats treated with MK extract (MK -200 and MK -400 groups) compared to diabetic control kidneys (Figure 3 F).

The islets of Langerhans of both control groups were normal in histological appearance; they were unevenly scattered in the pancreatic tissue and they were of varying sizes in the same lobule of the pancreas, the islet cells were closely situated close to capillaries (Figure 4 A). The pancreas of STZ diabetic rats showed atrophied islets with moderate degranulation and disin-



**Figure 3. Microphotographs of Kidney Sections. A; Control Showing Normal Architectures, B; STZ Diabetic Rat Showing Moderate Enlargement of Glomeruli, Dilatation and Congestion of Glomerular Capillaries (arrow), C; STZ Diabetic Rat Showing Atrophied Glomeruli (arrow) and Tubular Damage with Eosinophilic Materials (S) and Hemorrhage (H) in Blood Vessel, D; STZ Diabetic Rat Showing Degeneration of the Glomeruli (arrow) Associated with Mesangial Cells Hyperplasia and Hydropic Tubular Epithelium, Vacuolations and Tubular Dilatation (V), E; STZ Diabetic Rat Showing Interstitial Fibrosis (F) Associated with Destroyed Glomerulus (arrow) and Mononuclear Inflammatory Cells Infiltration (M), F; STZ Diabetic Rat Treated with Curry Leaf Showing Normal Looking Glomeruli (arrow) and Tubules. H & E. "A & B 200 x; C, D & F 100x; E 40x"**



**Figure 4. Microphotographs of Pancreas. A; Control Showing Normal Islets of Langerhans, B; STZ Diabetic Rat Showing Shrunken Islet with Degranulated  $\beta$ -cells, Hyaline Deposition and Congested Capillaries (arrow), C; STZ Diabetic Rat Showing Two Shrunken Islets with Degranulated  $\beta$ -cells, Hyaline Deposition, and Congested Capillaries (arrow), D; Pancreas of STZ Diabetic Rat Treated with Curry Leaf Extract Showing Normal Looking Appearance of the Islet Structure. H & E. "200x"**

tegration of  $\beta$ -cells, the endocrine cells were separated by empty spaces and hyaline masses and congested blood capillaries (Figure 4 B & C), fibrotic changes were observed at the periphery of the pancreatic islets (Figure 4 C). Treatment with MK extract to STZ diabetic rats stimulated significant improvement in degenerative changes induced by STZ injection in endocrine pancreas (Figure 4 D).

## Discussion

In the present study hyperglycemia was confirmed five days after STZ administration and immediately followed by daily treatment with graded dose (200 & 400 mg/kg) of MK aqueous extract for 30 days. There was a significant blood glucose lowering effect in diabetic treated rats as compared to normal controls; the maximum fall of 85% for the rats treated with MK-200 mg/kg on the 30th day was slightly above that of MK-400 mg/kg treated rats (83%). This phenomenon of dose independent response is common with indigenous plants as it has been observed with *Vinca rosea*,<sup>18</sup> the blood glucose lowering effect in normal rats was almost negligible (4%).

The present study has revealed a significant ( $p < 0.001$ ) loss of body weight in diabetic group when compared to the normal rats throughout the experiment. However, daily administration of MK aqueous extract for 30 days reversed the body weight to normal level. The normal

controls on the other hand, had a significant (55%) increase in body weight on 30<sup>th</sup> day in comparison to the experimental groups (16.3%, 17.3% and 19%). Thus, the result of our finding is in support of other literature reports; advocating the effectiveness of MK aqueous extract in partially attenuating the catabolic effects of STZ in diabetic rats, through reversal of the body weight loss.<sup>19</sup>

The present investigation revealed structural damage in the pancreatic islets and the kidney of the STZ treated rats. The pancreatic islets appeared atrophied with degenerated  $\beta$ -cells associated with hyaline deposition and congested blood vessels; these observations agree with previous investigations in rabbits,<sup>20</sup> rats,<sup>21,22</sup> and mice.<sup>7</sup> Hyper-trophy of the glomeruli and thickening of glomerular basement membrane associated with mesangial cells together with tubular damage and interstitial fibrosis was observed in the diabetic kidneys of the present study. These pathological changes are consistent with those observed in STZ diabetic rabbits, mice, hamsters, rats, and alloxan diabetic rabbits.<sup>6,12,20,23-25</sup>

In the present study, histopathological assessment of the diabetic islets treated with either dose (200 and 400 mg/kg) of MK for 30 day showed improvement in islet morphology; this was associated with the improved glucose levels and increased body weight observed in these animals. Our results are in agreement with previous studies using MK aqueous extract in STZ,<sup>26</sup> and alloxan induced diabetic rats.<sup>27</sup> Akinola *et al.*<sup>28</sup> observed improvement in islet's histological structure of STZ diabetic Wistar rats treated on (500mg/kg) ethanolic extract of the *Azadirachta indica* Leaves for 50 days. Diabetic rats treated daily with oral dose of 12.5 mg of *Anastatica hierochuntica* for two weeks showed significant improvement in the islet injury induced by STZ.<sup>29</sup> Restoration of the normal architecture of the pancreatic islet structure was observed in STZ diabetic treated with 200mg/kg of cinnamon aqueous extract for 30 days.<sup>30</sup>

*Terminalia arjuna* extract at the dose of 500 mg/kg body weight for 30 days was found to effectively improve the liver, kidney and pancreas function and reduced the lesions associated with diabetic state in alloxan diabetic rats.<sup>31</sup> Treatment of diabetic rats with 200 mg/kg *Triumfetta pilosa* Roth for 21 days prevented the histopathological alteration in kidney and caused a return to their normal structure.<sup>32</sup> Pronounced improvement in the renal function and reduced kidney lesions was detected in STZ diabetic rats treated with 300 mg/kg of *Anacardium occidentale* for 5 weeks.<sup>33</sup> In vivo studies demonstrated that curcumin (7.5 mg/kg/day) protected pancreatic islets from C57/BL6J mice against STZ-induced death or dysfunction.<sup>34</sup> These

variations may be related to species differences and/or the type and dose of the used medicinal plant, the duration of treatment and to the examined organ.

The precise mechanisms by which the medicinal plants induce improvement in the function and structure of the kidney and the pancreatic islets are inconclusive and insufficient data are available to make any generalized conclusion. The hypoglycemic action of the of herbal plants extract in STZ diabetic rats may be related to the insulinomimetic action or by inhibiting glucose absorption from intestine, stimulation of glucose uptake by peripheral tissue, or inhibition of endogenous glucose production from hepatocytes.<sup>35</sup> Two possible explanations for the protective effect of *Aloe vera* in STZ diabetic rats have been suggested by preventing the death of the cells and/or second, it may permit recovery of partially destroyed cells.<sup>36</sup>

The efficacy of oral fed MK aqueous extract in improving the parameters of renal function (serum urea and creatinine) was estimated in STZ diabetic rats.<sup>16</sup> These changes in diabetic animals were presumably suggested to be as a result of increased oxidative stress. Curry leaf extract helps reduce oxidative stress on pancreatic cells by restricting the action of pancreatic alpha-amylase enzymes. The aqueous slurry of dried leave powder of this herb is useful in combating diabetes and serving as a potential hypoglycaemic agent without preparing any organic solvent extract.<sup>26</sup> The mode of action *Murraya koenigii* has been suggested to be either due to increased glycogenesis or decreased glycogen-nolysis or gluconeogenesis and/or due to insulin secretagogue effect of MK, which causes an increased glucose uptake and its consumption by cells.<sup>17</sup> The characterization of the active principle responsible for the antihyperglycemic activity of MK has not yet been elucidated. However, "carbazole alkaloid" which has anti-hyperglycaemic and antihyperlipidaemic activity, has been found in the leaves of MK.<sup>16</sup> The present study also corroborates with several literature reports that claim an anti-hyperglycaemic effect of MK in different animal models.<sup>15,37</sup> It is possible that MK may have direct or indirect effect on insulin release. Radioimmunoassay studies are needed to elucidate the effect of MK treatment on insulin and other hormones "related to glucose metabolism" secretion. Further electron microscopic investigations on the kidney and the pancreatic islets of STZ diabetic rats treated with MK are in progress.

## Conclusions

It is concluded from the present study that MK extract shows hypoglycaemic activity and renal and endocrine protective effects in STZ diabetic rats.

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## Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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