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Protective effect of betanin against streptozotocin - nicotinamide induced liver, kidney and pancreas damage by attenuating lipid byproducts and improving renal biomarkers in Wistar rats

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Abstract

Objective: We attempted to determine whether betanin (from natural pigments) that has antioxidant properties would be protective against diabetes induced by streptozotocin- nicotinamide in adult Wistar rats. **Methods:** Diabetes was induced by a single intraperitoneal (i.p.) injection of streptozotocin (STZ; 45 mg/kg b.w.) dissolved in 0.1 M citrate buffer (pH 4.5) 15 min after the i.p. administration of nicotinamide (NA; 110 mg/kg b.w.). Experimental rats were administered betanin at the dose of 20 mg/kg b.w. and glibenclamide (600 µg/kg b.w.) once a day for 30 days. **Results:** Untreated diabetic rats showed significantly increased levels of plasma glucose, thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides (LOOH), urea, uric acid, creatinine and decreased levels of plasma insulin. Co-administration with betanin to the diabetic rats showed improved levels of plasma glucose, insulin, lipid peroxidation byproducts (LPO) and kidney biomarkers enzymes when compared to untreated diabetic rats. Moreover, histological study of kidney revealed the effect of betanin in diabetic rats. Similar kind of experimental results were obtained in glibenclamide treated diabetic rats. **Conclusion:** According to our current study, betanin had a beneficial role against the diabetes induced by STZ-NA in rats.

Keywords: Betanin; Lipid byproducts; Streptozotocin – Nicotinamide; Diabetes mellitus.

1. Introduction

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by common feature of chronic hyperglycemia with disturbance in the metabolism of carbohydrate, fat and protein. Moreover, the impaired metabolism leads to the progression and aggravation of oxidative stress through several mechanisms, such as glucose autoxidation, protein glycation and AGEs formation leading to the development of secondary

diabetic complications i.e. nephropathy, retinopathy, neuropathy, macro and microvascular damages. According to World Health Organization (WHO) report the amount of people by diabetes has increased from 108 million in 1980 to 422 million in 2014; while global occurrence of diabetes amongst adults above 18 years of age has risen to 8.5% in 2014 from 4.7% in 1980 (WHO, 2016). Insofar as India is concerned presently about 62 million people are affected by DM and it ranks second to China which harbour's 92.3 million diabetics (Victor et al., 2016).
Diabetic nephropathy is a single leading cause of end stage renal disease (ESRD) and is a medical devastation worldwide in which oxidative stress plays a significant role in the kidney impairments such as acute and chronic renal failure, glomerular injury and obstructive nephropathy (Baliga et al., 1999, Fiorillo et al., 1998). Various studies have demonstrated that the supplementations of antioxidants are known to attenuate free radical mediated diabetic nephropathy (Hahn et al., 1999, Melhem et al., 2001, Anjaneyulu et al., 2004). Thus, the agent that restrains the detonated production of reactive oxygen species (ROS) might alleviate the oxidative stress thereby protecting the kidney tissues.

Unlike other pigments betalains are not well studied with regard to their pharmacological properties and mechanism of action. Betalains are pigments present in red beetroot

(*Beta vulgaris var. rubra)* and a number of other species e.g amaranthus, rose and cactus pear (Vulic et al., 2014). Among betalain components, betanin (betanidin 5-O-β-D-glucoside, CI Natural Red 33, CAS number: 7659-95-2) is the most abundant (Gliszczynska-Swigło et al., 2006). According to the German regulation on food additives betanin is permitted "quantum satis" as a natural red food colorant (E-number E 162). e.g. dairy products and pharmaceuticals (Georgiev et al., 2010). It comprises a phenolic and cyclic amine groups, which are good donors of electron that endow it with exceptionally high free-radical scavenging ability, and betanin can distribute inside of cells.

Numerous studies have reveals the beneficial role of betanin such as anti-inflammatory (Allgera et al., 2005), anti-proliferative effects (Sreekanth et al., 2007), strong antioxidant (Sutaria et al., 2017), anticarcinogenic (Kapadia et al., 2011), inhibits lipid peroxidation (Kanner et al., 2001), nephroprotective (Tan et al., 2015) and cardioprotective activity (Han et al., 2015). Betanin also exhibits gene regulatory activity partly via nuclear factor erythroid 2-related factor 2 (Nrf2) - dependent signaling pathways in hepatocytes (Krajka-Kuzniak et al., 2013). Recently, we have reported that betanin protects the hepatic tissue and restore the carbohydrate metabolism in experimental rats (Indumathi et al., 2017). However, none of the study reported the beneficial effect of betanin on the protection of diabetic kidney in the STZ-NA induced rats. The current study was designed to elucidate the therapeutic potential of betanin exhibits additional pharmacological effects on lipid byproducts and kidney biomarkers enzymes in both normal and STZ-NA induced diabetic rats. The effects made by these treatments are compared with standard drug glibenclamide.

2. Materials and Methods

2.1. *Chemicals*

Streptozotocin (STZ), Nicotinamide (NA) Betanin (CAS Number: 7659-95-2, Formula: $C_{24}H_{26}N_2O_{13}$) and Glibenclamide were purchased from Sigma-Aldrich (St. Louis, MO, USA) The rest of the chemicals were obtained from Hi Media (Mumbai, India) and SD-Fine Chemicals (Mumbai, India) were of analytical grade. All the biochemical analyses were carried out according to the instructions of the related reagent kits.

2.2. *Experimental induction of diabetes*

Diabetes was induced in rats by a single i.p. injection of freshly prepared STZ (45 mg/kg b.w.) in 0.1 M citrate buffer (pH 4.5) 15 min after the i.p. administration of 110 mg/kg b.w. NA. 72 h after STZ administration, rats with blood glucose concentration >250 mg/dL were considered diabetic and were included in the study. The treatment was started on the third day after STZ-NA injection which was considered as the first day of treatment.

2.3. *Experimental animals*

Male Albino Wistar rats weighing around 180-210 g were acquired from Rajah Muthiah Medical College, Annamalai University and were housed in stainless steel screen bottom cages under standard conditions (12 h light/dark cycle, ambient temperature of 25± 2 ˚C). The rats were allowed free access to standard diet (Hindustan Lever Ltd, Bangalore, India) and water *ad libitum.* The rats were acclimatized to the laboratory environment for three days. The experimental design was performed in accordance with the current ethical norms approved by

the Institutional Animal Ethics Committee Guidelines (Reg No. 160/1999/CPCSEA, Proposal No: 1105, 2014) Annamalai University, for the investigation of experimental pain in conscious animals

2.4. *Experimental design*

The study was aimed to observe the effects of betanin on antioxidant in STZ-NA induced diabetic rats. In this experiment, a total of 30 rats (18 diabetic surviving rats, 12 normal rats) were used. Betanin was dissolved in water and administered via oral intubation to the experimental rats using a gavage needle daily for a period of 30 days. The rats were randomly assigned to five groups each consisting of six rats. The groups were treated as follows:

At the end of the experimental period, all the rats were fasted overnight, sacrificed by cervical decapitation. The blood was collected with or without anticoagulant for plasma or serum separation, respectively.

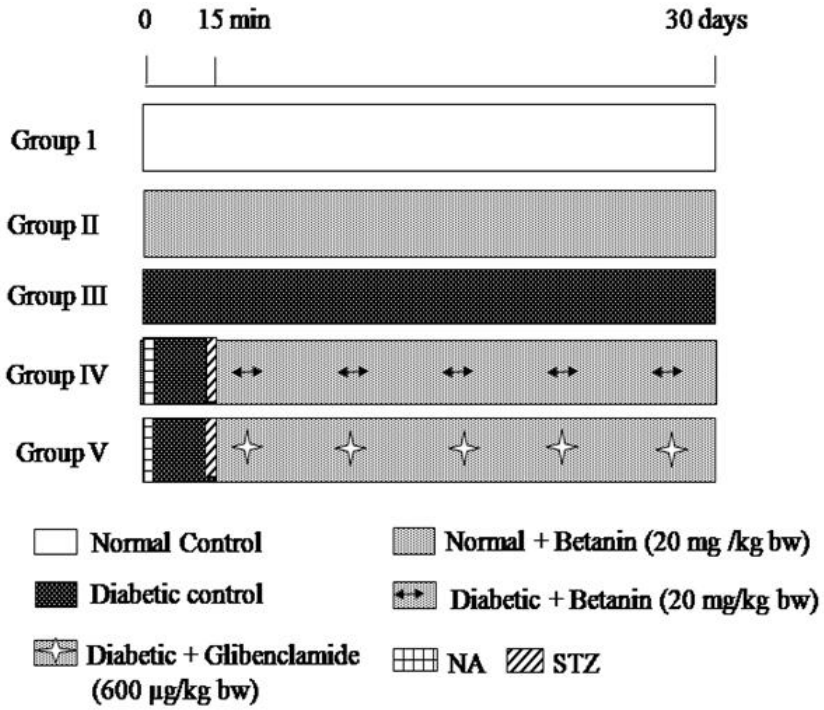

Fig. 1 Experimental design

2.5. *Analytical procedure*

2.5.1. *Analyze the activities of plasma glucose and insulin*

The estimation of glucose was done by the methods of Tinder (1969) using a commercial kit (Agape Diagnostics Pvt. Ltd., India). Plasma insulin was estimated using a commercial kit by ELISA.

2.5.2. *Estimation of thiobarbituric acid reactive substances (TBARS)*

The concentration of TBARS in the plasma and tissues was estimated by the method of Niehaus and Samuelson (1968). 0.5 mL of plasma or tissue homogenate was diluted with 0.5 mL of double distilled water and mixed well, and then 2.0 mL of TBA-TCA-HCl reagent was added. The mixture was kept in a boiling water bath for 15 min, after cooling, the tubes were centrifuged at 1500 x g for 10 min and the supernatant was measured. A series of standard solution in the concentrations of 2-10 nmol were treated in a similar manner. The absorbance of the chromophore was spectrophotometrically read at 535 nm against blank.

2.5.3. *Evaluation of Lipid hydroperoxides*

Lipid hydroperoxides in the plasma and tissues were estimated by the method of Jiang et al. (1992). 0.9 mL Fox reagent was mixed with 0.1 mL of the plasma or tissue homogenate, incubated for 30 min at room temperature and the absorbance was spectrophotometrically read at 560 nm against blank.

2.5.4. *Assessment of Urea*

Serum urea was estimated by using the diagnostic kit based on the method of Fawcett and Scott (1960). To 1 mL of buffered enzyme, 10 µL of sample was added, mixed well and kept at 37 °C for 5 min. 10 µL of distilled water (blank) was also processed simultaneously. To all the tubes about 1mL of colour developing reagent was added and mixed well. After incubation for 5 min at 37° C, 1 mL of distilled water was added and the colour developed was read at 600 nm.

2.5.5. *Measurement of uric acid*

Serum uric acid was estimated by using the diagnostic kit based on the enzymatic method described by Caraway (1955). To 1 mL of the enzyme reagent, 25 µL of sample was added and mixed by inversion, 25 µL of distilled water (blank) was also processed simultaneously. The tubes were incubated at 37° C for 5 min and the colour developed was read at 510 nm.

2.5.6. *Estimation of Creatinine*

Serum creatinine was estimated using the diagnostic kit based on Jaffe's (1886) method. 0.1 mL of serum was added to a reagent mixture containing 0.5 mL picric acid solution and 0.5 mL of NaOH. The tubes were mixed well and left aside for 20 min. With the spectrophotometer adjusted to zero absorbance with distilled water, readings were recorded was taken at 510 nm at 20 min (A_1) and exactly after 45 min (A_2) for the test and standard, which was used to determine the creatinine concentration in the test sample.

2.6. *Histopathological study*

The sacrificed animals were quickly dissected. Kidney tissues were harvested and were fixed in 10% neutral formalin solution for 24 h followed by washing, dehydration by passing successfully in different mixture of ethyl alcohol-water clearing in xylene and embedded in hard paraffin. The tissue sections were cut (5 µm thickness) stuck on clean slides. Sections were stained with hematoxylin and counterstained by 0.5 aqueous eosin dye which was mounted in neutral deparaffinated xylene medium for microscopic observations (Olympus CX41, Olympus Corp, Tokyo, Japan).

2.7. *Statistical Analysis*

Experimental results were expressed as means ± SD and subjected to one-way analysis of variance (ANOVA), using a computer software package (Statistical Package for the Social Sciences, SPSS version 15.0; Cary, NC) and the comparisons of significant differences among the groups were performed using the Duncan's Multiple Range Test (DMRT; Duncan, 1957). All the results were statistically significant if the p value is less than 0.05.

3. Results

3.1. *Effect of betanin on plasma glucose and insulin levels*

Figure 2 illustrate the levels of plasma glucose and insulin in control and experimental animals. The levels of plasma glucose were markedly increased whereas plasma insulin levels were significantly ($p < 0.05$) decreased in diabetic control rats. The co-administration of betanin (20 mg/kg b.w.) to diabetic rats prevented significantly the raise of glucose level and also reversed the levels of insulin ($p < 0.05$) compared with untreated diabetic rats. However, the supplementation of betanin to normal rats resulted in no significant ($p < 0.05$) changes in the levels of glucose and insulin when compared with normal control rats.

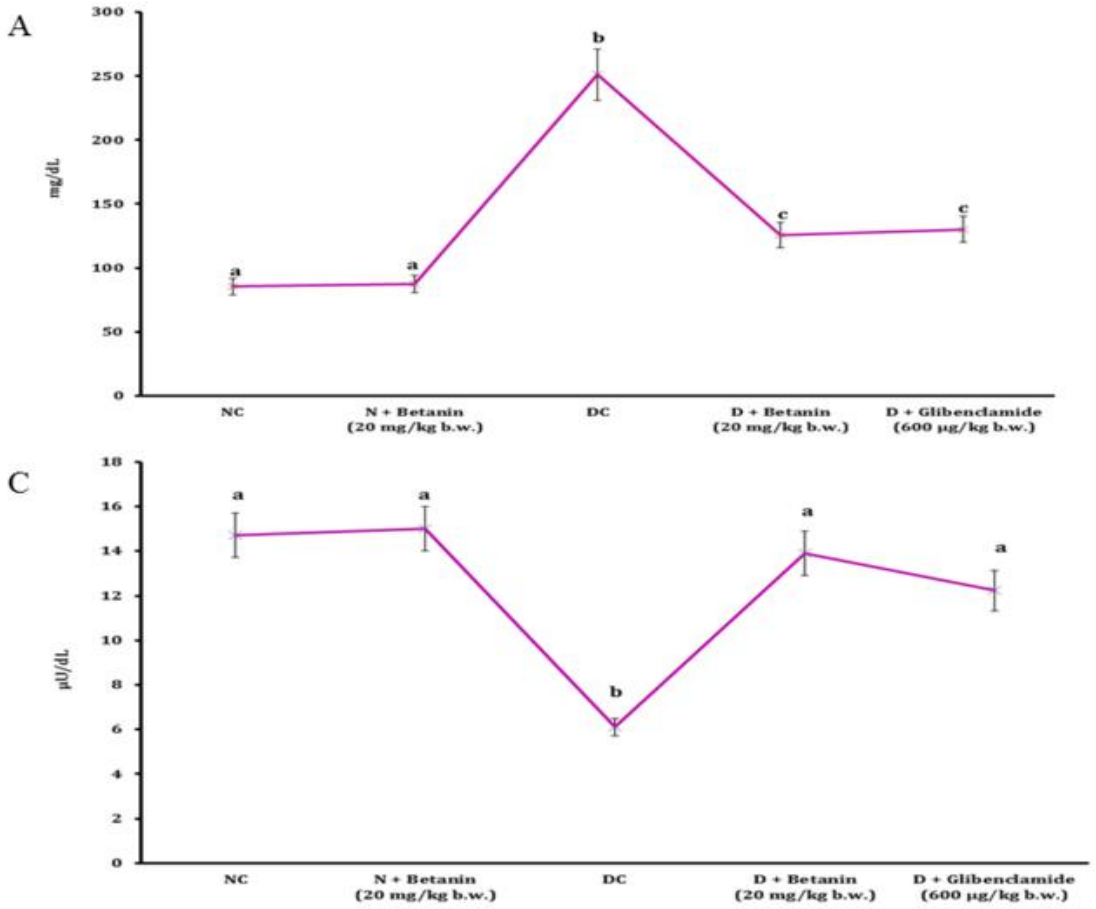

Fig. 2Changes in the levels of plasma glucose and insulin in normal and experimental rats.
Each column is mean ± standard deviation for six rats in each group. Values not sharing a common marking (a–e) differ significantly at $p < 0.05$ (DMRT).

3.2. *Effect of betanin on LPO markers in plasma and tissues*

The results revealed that the LPO by-products such as TBARS and LOOH were not altered in betanin alone treated rats. In comparison with normal rats, significantly enhanced levels of LPO by-products were observed in plasma and tissues such as liver, kidney and pancreas of STZ-NA induced diabetic rats which show the higher LPO. On the contrary, STZ-NA induced diabetic rat treated with betanin (20 mg/kg b.w.) along with glibenclamide (600 µg/kg b.w.) were extensively curtailed the levels of LPO by-products in the plasma and tissues when compared to diabetic rats as shown in Figure 3 & 4

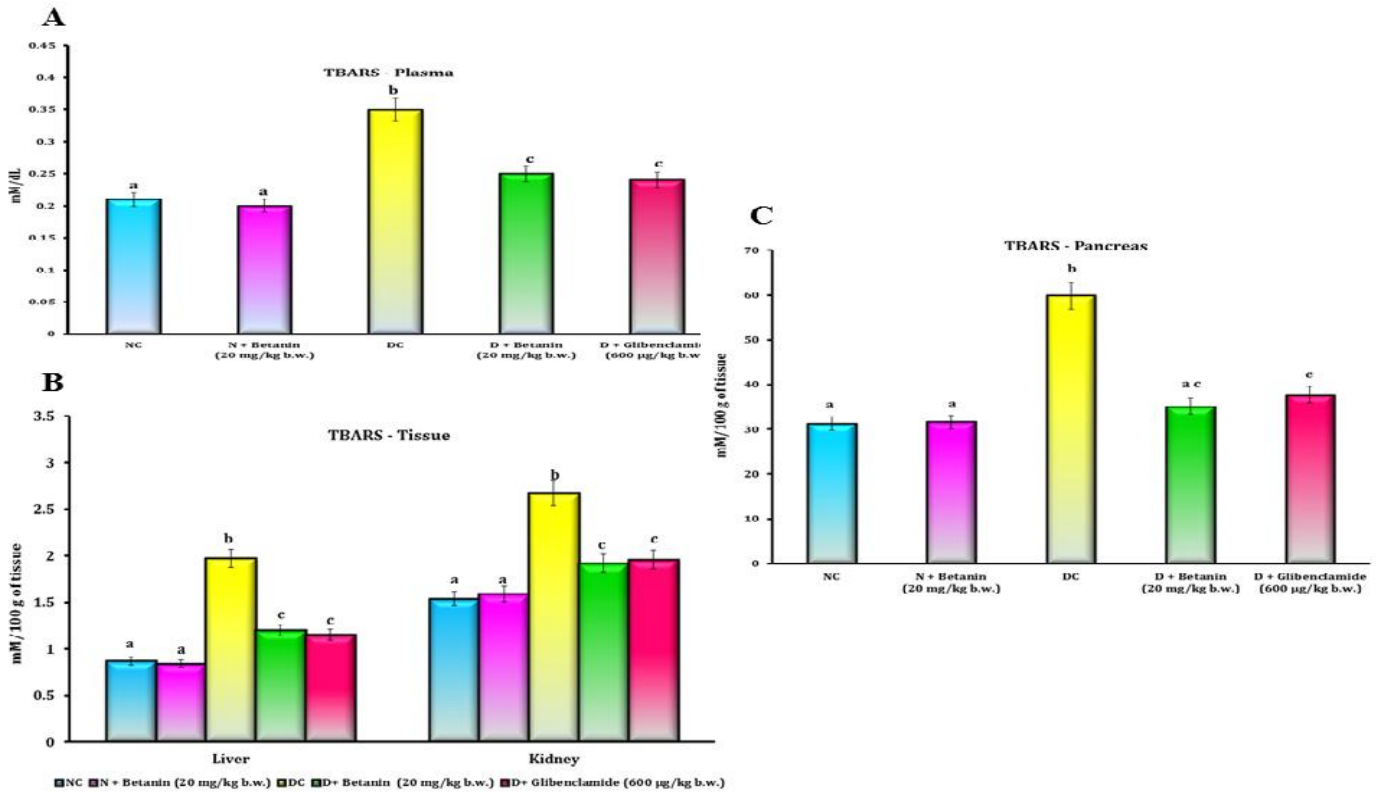

Fig. 3 Changes in the levels of plasma and tissue TBARS in normal and experimental rats

Values are expressed as mean ± S.D for 6 rats in each group. Values not sharing common alphabet differ significantly at $p < 0.05$

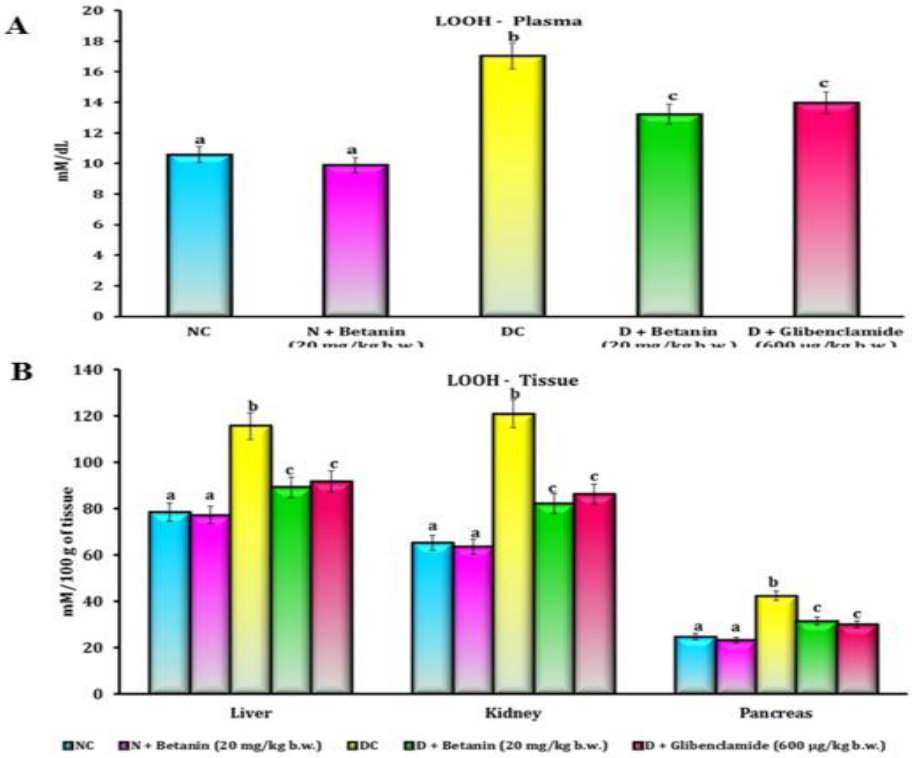

Fig. 4 Changes in the levels of plasma and tissue LOOH in normal and experimental rats

Values are expressed as mean ± S.D for 6 rats in each group. Values not sharing common alphabet differ significantly at $p < 0.05$

.3. *Changes in the levels of urea, uric acid and creatinine*

The results obtained from the present study revealed that STZ-NA induced diabetic rats had potentially elevated the levels of serum renal biomarker enzymes such as urea, uric acid and creatinine as compared to normal rats. On the other hand, subsequent treatment with betanin (20 mg/kg b.w.) showed considerably decreased levels of serum urea, uric acid and creatinine as compared with diabetic rats**.** Similar kind of experimental results were observed in the glibencalmide (600 µg/kg b.w.) treated rats. Although**,** betanin (20 mg/kg b.w.) alone treatment did not show any changes in the above mentioned results as compared to normal rats (Figure 5).

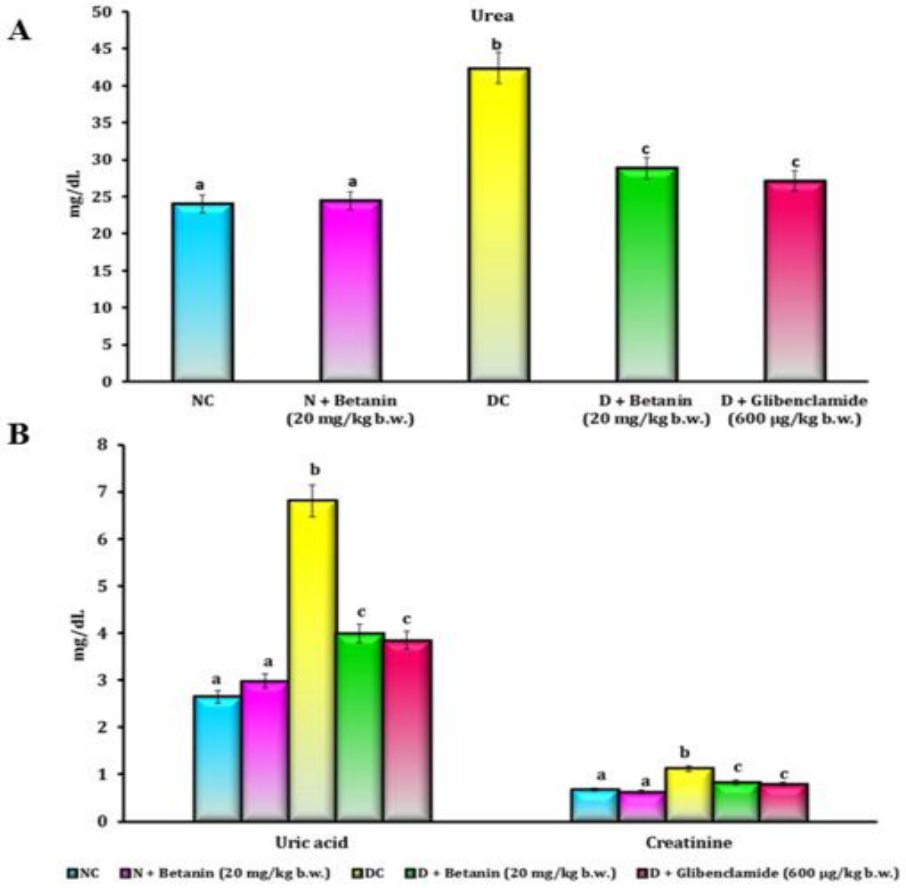

Fig. 5 Changes in the levels of renal biomarker enzymes in normal and experimental rats.
Values are expressed as mean ± S.D for 6 rats in each group. Values not sharing common alphabet differ significantly at $p < 0.05$.

3.4. *Histological observation*

Figure 6A-E portrays the photomicrographs of H&E staining of kidney tissue of control and experimental rats. Normal rats showed the normal architecture of the renal tissues. Kidney section of diabetic control rat showed proximal tubular necrosis, mesangium expansion, swelling of tubules and glomeruli enclosed by packed cells. Betanin (20 mg/kg) and glibenclamide (600 µg/kg) treated rats decreased the above mentioned pathological changes in the kidney. No histological alterations were observed in normal and betanin alone treated rats.

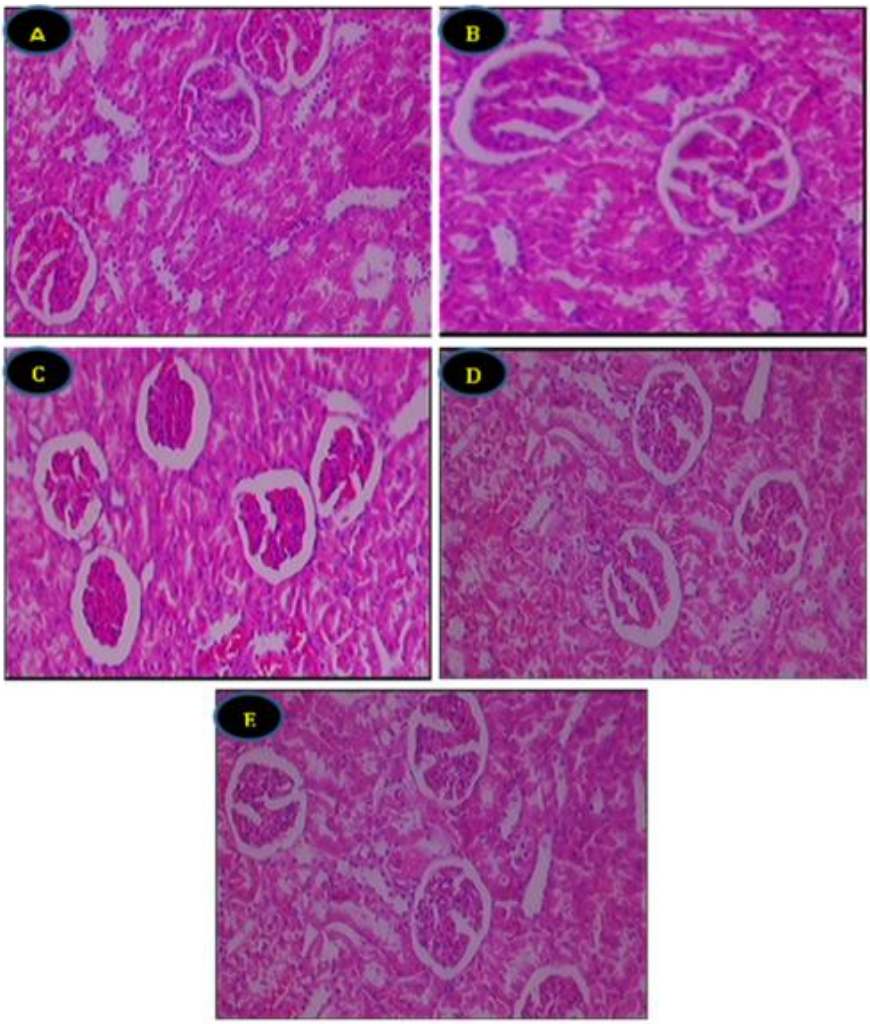

Fig. 6 Photomicrograph of histological observation of kidney in normal and experimental rats.
(40x)(A) Normal rats (B) Rats treated with betanin (20 mg/kg b.w.) alone (C) Rats treated with STZ-NA (D) Rats treated with STZ-NA and betanin (20 mg/kg b.w.) (E) Rats treated with STZ-NA and glibenclamide (600 µg/kg b.w.). The diabetic kidney shows the glomeruli enclosed by tightly packed cells, proximal tubular necrosis and mesangium expansion. Supplementation of betaninreinstates the induced pathological changes of kidney.

4. Discussion

In the present study, we evaluated the effects of betanin on renal tissues in STZ-NA induced diabetic rats. In recent years, natural phytochemical constituents have been shown to have the potential to treat DM. Attention has been notably focused on diet rich in natural pigments, which generally have shown antioxidant and antidiabetic effects. The natural pigment betanin administration and glibenclamide knowingly decreased the blood glucose level and improved the insulin level. Betanin might be enhanced the glucose utilization by the peripheral tissues either by promoting glucose uptake and metabolism by increasing insulin secretion.

Hyperglycemia prompts protein catabolism a significant elevation in the levels of urea, uric acid and creatinine which is considered as standard markers of renal dysfunction. One of the major nitrogen containing metabolic products of protein is urea. During the diabetic conditions, the noticeable deprivation of proteins leads to the excessive accumulation of urea in the systemic circulation than its excretion (Elizabeth, 2005). In diabetes, due to the elevated concentration of glucose, damages occur in kidney causing impairment in renal function resulting in the accumulation of nitrogenous wastes in circulation (Almdal and Vilstrup, 1988). The protein glycation during diabetes is associated with muscle wasting and thereby, an increased release of purines.

The elevated levels of purine nucleotides are the main source of uric acid, an endogenous water soluble antioxidant, has been thought to be a metabolically inert end product of purine metabolism by the increased activity of xanthine oxidase (Madianov, 2000). Creatinine is an energy storage compound in the muscles. It is endogenously produced and released into body fluids and its clearance measured as an indicator of glomerular filtration rate (GFR). Hyperglycemia leads to an increased production of glomerular matrix proteins, the accumulation of which decreases the surface area for filtration leading to declined GFR. Increased creatinine in diabetic rats is taken as an index of altered GFR in diabetic nephropathy. In current study, a considerable elevation in the kidney biomarker enzymes was observed. The co-administration of betanin decreased the levels of urea, uric acid and creatinine in STZ-NA induced diabetic rats, recovered renal function, which is due to improved glycemic control thereby it elicits the renoprotective nature of betanin which is reinforced by our histological findings (Fig. 5D) in STZ-NA rats. Our results were concomitant with Tan et al (2015) who reported that betanin have effect on serum markers for kidney acute injuries, including urea, uric acid and creatinine in rats.

Free radical-induced lipid peroxidation has been associated with a variety of disease process including diabetes mellitus (Saddala et al., 2013). When the antioxidant enzymes activity is reduced, superoxide anion and H_2O_2 are extremely available in biological systems, stimulating the ROS production and the propagation of lipid peroxidation (Muthuraman and Srikumar, 2010). Thiobarbituric acid reactive substances (TBARS) and lipid peroxide (LOOH) are the markers of lipid peroxidation. It is an autocatalytic reaction which leads to oxidative destruction of cellular membranes, resulting in the production of toxic free radicals such as, superoxide radicals, H_2O_2 and hydroxyl radicals (Yassa and Tohamy, 2014). Measurement of TBARS was used as an index of lipid peroxidation and it helps to assess the extent of tissue damage (Jangale et al., 2013). Several studies have reported an increase in TBARS in the plasma, liver, kidney and pancreas of diabetic rats (Nain et al., 2012). Countless studies described that oxidative stress interact with polyunsaturated fatty acids, that leads to the formation of lipid byproducts, which causes damage to the membrane components of the tissues (Arya et al., 2014). STZ-NA induced experimental diabetes resulted in the elevated levels of lipid peroxides by oxidative degradation of polyunsaturated fatty acids (Eliza et al., 2010). Increased lipid peroxidation plays an important role in the progression of diabetes by altering the trans-bilayer fluidity gradient, which could hamper the activities of membrane-bound enzymes and receptors (Noctor et al., 2015).

In our study, there were significant increase in lipid peroxidation by products in the plasma and tissues of diabetic rats. The increase in oxidative stress markers result from the toxic effect of ROS produced during chronic hyperglycemia (Evans et al., 2002). Co-treatment with betanin to diabetic rats resulted in a notable reduction in the levels of lipid peroxidation byproducts which may be due to its free radical scavenging effect and as a result of improved glycemic control. According to our findings Kanner et al (2001) who reported that betanin also inhibits lipid peroxidation *in vitro* in extremely at small concentrations.

5. Conclusion

Summing up, the present study we demonstrates that oral intubation of betanin; a natural betacyanin pigment from the red beetroot considerably decreased the peripheral glucose and improved the insulin secretion and alters the levels of lipid byproducts and kidney biomarkers through its insulinotropic effect in STZ-NA induced type 2 diabetic rats. However, further studies on the molecular action of betanin are under progress.

Disclosure statement

The authors declare that they have no conflicts of interest concerning this article.

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