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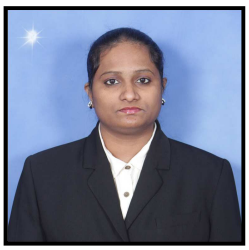

# PROTECTIVE EFFECTS OF NARINGENIN ON STREPTOZOTOCIN-INDUCED DIABETIC NEPHROPATHY IN RATS

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## ABSTRACT

Diabetic nephropathy is one of the serious diabetic complications and has been a major cause of end-stage renal disease which requires dialysis or transplantation. The role of oxygen radicals are known for the pathogenesis of kidney damage. There are several recent studies focusing positively on therapeutics of diabetic nephropathy using traditional herbal medicines. This study adopted oral administration of naringenin to determine the protective effects of it on improving antilipid perxidative and antioxidants. Total of 24 male Wistar rats were divided into 4 groups as follows: control, diabetic nephropathy (DN), DN+naringenin and naringenin alone. The altered body weight and kidney weight of DN induced animals were normalized in naringenin treated rats. There is no significant difference in naringenin alone treated groups. The increased lipid peroxidation and decreased antioxidants (GSH, GPx, SOD, CAT, and GST) levels were found in group II DN rats. The altered oxidative stress markers were normalized in naringenin administered groups. The changes suggestive of dilation of tubules necrosis and swelling of the epithelial cells with slight loss in brush border integrity were found in the kidney tissue of DN induced animals. The naringenin treated animals were normalized histopathological changes. We conclude that naringenin have protective effects against DN due to its antilipid peroxidative effects.

## KEYWORDS

Lipid peroxidation, Kidney, Naringenin, Antioxidants, Diabetic and Nephropathy.

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## INTRODUCTION

Diabetic nephropathy (DN) is one of the alarming worldwide health problems at present leading to micro vascular (retinopathy, neuropathy and nephropathy) and macro vascular (heart attack, stroke and peripheral vascular disease) complications in many countries of the world[1]. DN affects approximately one-third of all diabetic

patients. Most devastating complication of diabetes is nephropathy, which causes 14% of all deaths in diabetes patients and accounts for 40% of end-stage renal cases[2, 3]. DN is the common cause of chronic kidney failure and end stage of renal disease[4]. Several factors, such as hyperglycemia, hyperlipidemia, oxidative stress and inflammatory cytokines, contribute to the progression of renal damage in DN[5, 6]. Diabetic nephropathy results from the combined effects of various genetic and environmental factors. Prolonged duration of diabetes, poor glycaemic control and hypertension are major risk factors for both diabetic nephropathy and cardiovascular disease[7, 9].

Flavonoids are a group of natural products present mainly in plants and plant products with diverse chemical structure and have been identified in several studies for their various biological actions[10]. They are widely recognized as naturally occurring antioxidants that can inhibit lipid oxidation in biological membrane. They usually contain one or more aromatichydroxyl groups, which is responsible for their antioxidant activity[11]. Naringenin is a flavanone compound found in citrus fruits, such as grapes and oranges, and also in tomato skin. It has been pharmacologically evaluated for antioxidant[12], anti-inflammatory[13] and anticancerous[14]. Antiatherosclerotic[15], hepatoprotective [16], nephroprotective[17] and immunomodulatory[18] activities. Naringenin effectively quenches free radicals due to a 4'hydroxyl group in its ring 11. However, to our knowledge no reports have recorded the precise biological action of naringenin against on diabetic nephropathy in rats. Therefore, the present study was designed with an aim to determine the protective effects of naringenin on diabetic nephropathy in rats.

## MATERIALS AND METHODS

### Animals

Male albino Wistar rats ((130-140g) were used for the study. The animals were acclimated to laboratory housing conditions under 12hr light and dark cycles for 2 weeks prior to the commencement of the treatment under standard laboratory conditions (Room temperature 25±2°C and relative humidity 50–60 %). They were housed in polypropylene cages with stainless steel grill top, bedded with rice husk and offered commercial standard pellet diet and tap water ad libitum. The animals used in the present study were maintained in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

### Chemicals

(±) Naringenin (95%) and streptozotocin were procured from Sigma Chemical Co. (St. Louis, Missouri, USA), stored at 2-4°C and protected from direct sunlight. All other chemicals used were purchased from standard local commercial suppliers and were of analytical grade.

### Experimental protocol

The adult Wistar albino rats were divided into four groups with six animals in each group and given dose regimen as given below.

Group I. Control rats treated with vehicle alone. Group II. Streptozotocin (STZ) induced diabetic nephropathy, the animals were fasted overnight and diabetes was induced by a single intraperitoneal (i.p.) injection of freshly prepared STZ (55 mg/kg body weight of rats) in 0.1 M citrate buffer (pH 4.5). The animals had free access to 5% glucose solution over night to overcome the drug induced hypoglycemia. Group III. Animals were induced diabetic nephropathy as group II treated with naringenin (50mg/kg body weight/day) suspended in 0.5ml carboxy methylcellulose daily using intragastric tube for 15 days orally. Group IV. Animals treated with naringenin (50 mg/kg body weight) dissolved in 0.5ml carboxy methylcellulose daily using intragastric tube for 15 days orally.

### Preparation of the samples

At the end of the experimental period the animal were fasted overnight and were sacrificed by cervical decapitation. The blood was collected and serum was separated by centrifugation at 3,000 rpm and stored at -20ºC and used for the various biochemical and enzyme analysis. The animals were quickly dissected kidney were excised and perfused with ice cold saline. A part of kidney tissues were

used separately to prepare 10 % (w/v) homogenate in 0.1 M Tris–HCl buffer (pH 7.4) and centrifuged at 7,000 rpm for 10 min at 4ºC. The supernatant was used for the assays.

**Estimation of biochemical parameters**

The level of urea and creatinine in serum samples was estimated spectrophotometrically according to the standard procedures using commercially available diagnostic kits (Sigma Diagnostics (I) Pvt Ltd., Baroda, India). The kidney homogenates were used for the measurement of Lipid Peroxidation (LPO) in terms of thiobarbituric acid reactive substance (TBARS)[19], reduced glutathione (GSH)[20], Superoxide Dismutase (SOD)[21], Catalase (CAT)[22], glutathione-S-transferase (GST)[23] and glutathione peroxidase (GPX)[24].

**Histopathological study**

For histological examination, kidney tissues were collected from all groups, then washed in ice-cold normal saline, cut into small pieces and fixed in 10% formalin for 24 h and processed further. 10 X 5 X 3 mm sized tissue blocks of both the organs were processed for paraffin embedding. Thin sections of 4–5µm thickness were cut with rotary microtome and stained with hematoxylin and eosin (H and E). The sections were observed under light microscope and photographs were taken at different magnifications.

**Statistical Analysis**

All data were expressed as Mean ± Standard deviation (n=6). The statistical significance was evaluated by one-way analysis of variance (ANOVA) using SPSS 12.5 and Duncan's Multiple Range Test (DMRT) obtained the individual comparisons. Values were considered statistically significant when $p<0.05$.

## RESULTS

Figure No.1 and 2 describe the effect of body and kidney weight of the control and experimental animals. Body weights was significantly decreased in group II diabetic nephropathy induced animals when compared to control group I animals ($p<0.05$). On the other hand body weight was significantly increased in naringenin treated animals ($p<0.05$) when compared with group II animals. The kidney weight was increased slightly in group II diabetic nephropathy induced animals ($p<0.05$) when compared to the group I animals. There was a mild decrease in the kidney weight of group III drug treated animals when compared with group II. On the contrary, no statistical differences were observed in both body weight and kidney weight of group IV drug control animals.

Table No.1 represents the levels of serum urea, uric acid, creatinine and protein of control and experimental animals. Due to diabetic nephropathy in group II animals urea, uric acid, creatinine and protein were increased in serum ($P<0.05$), when compared with group I control animals. Management with naringenin significantly reverted back these levels ($P<0.05$) in group III animals compared with group II animals. No remarkable changes were noted in group IV naringenin alone treated animals when compared with group I control animals.

Table No.2 demonstrates the effect of naringenin on lipid peroxidation and antioxidants in the kidney of control and experimental animals. The levels of LPO were found to be significantly increase than in group II DN induced animals ($p<0.05$) when compared with control animals under basal conditions. On the other hand, the administration of naringenin significantly diminish the peroxidation reaction in group III animals when compared with group II animals ($p<0.05$). However, no significant changes were observed in group IV drug control animals when compared to the group I control animals. Group II DN animals showed a significant decrease in the activities of enzymic antioxidants ($p<0.05$) and non-enzymic antioxidants ($p<0.05$). The levels of these antioxidants enzymes were increased significantly in naringenin treated group III animals when compared to that of group II animals ($p<0.05$). No remarkable changes were observed in group IV drug control animals when compared with control group I animals.

Histopathological studies on kidney of control and experimental animals are presented in Figure No.3. The kidney of control rats showed no abnormality.

Histological examination of kidney section showed marked and varying morphological alterations in DN induced animals comprise of vacuolation, tubular atrophy, severe tubular necrosis and interstitial inflammation. Naringenin treatment decreases the induced tubular necrosis and most of the changes and kidney displayed an almost normal architecture. The drug control group kidney showed normal architecture.

Figure No.3: Histopathological changes in the kidney tissue of control and experimental groups. A-Control (group I) shows renal parenchyma with normal glomeruli and tubules. B-Diabetic Nephropathy induced (group II) depicts changes suggestive of dilation of tubules necrosis and swelling of the epithelial cells with slight loss in brush border integrity. C- DN+naringenin intact tubular epithelium with mild swelling and focal fibrosis (group III). D-naringenin alone treated rat (group IV) shows reveals features similar to normal. H and E staining, magnification X 100.

## DISCUSSION

Traditional Indian and Chinese medicine are being increasingly recognized worldwide. A series of bioactive compounds have been isolated from the medicinal herbs. Citrus fruits are considered to have renal protective activity. After thorough analysis, we founds naringenin was the major active ingredient in the citrus fruits. Aim to evaluate this effect of naringenin; we established an animal model of diabetic nephropathy (DN) to assess its potency. DN also known as diabetic glomerulosclerosis or diabetic kidney disease is a frequently occurring and dangerous complication of diabetes mellitus[25]. DN has been recognized to be the leading cause for the end-stage renal disease (ESRD), accounting for nearly 50% of all new ESRD cases in the United States[26], and most patients with ESRD have to receive renal replacement therapy through either dialysis or kidney transplantation due to the diabetic renal failure in the end. With the changes of working and living styles, as well as the unhealthy dietary habits, the DN incidences have rapidly increased worldwide in the past few decades, and become a serious health concern to both individual and public[27, 28]. Oxidative stress has an important role in the pathogenesis of diabetes-induced nephropathy[29]. Previous studies on antioxidant administration to diabetic rats emphasized their hypoglycemic effects in STZ-induced diabetes[30,33]. The aim of the present study was to investigate the protective effects of naringenin, against diabetic renal damage primarily by microscopic and biochemical methods. Body weight loss is commonly observed[34,35] in group II experimental diabetes studies. Interestingly, previous report shows have reported that natural and chemical agents having free radical-scavenging properties prevented weight loss in diabetic rats[36,37]. Body weight loss in diabetic rats has been found to be related with muscle loss due to over catabolism of tissue proteins as a result of hyperglycemia[37]. In the present study, naringenin administered maintain the body weight by controlling blood glucose level thereby preventing protein catabolism. In the experimental diabetes studies, results on kidney weights are contradictory. Our studies show the kidney weight have increased like Garman *et al* reports but Cold iron *et al*. reported decreases in kidney weights[34,31], whereas Teoh *et al*. found no significant difference in kidney weights[38]. We observed that increased blood urea nitrogen and serum creatinine in diabetic rats indicates progressive renal damage, which is taken as an index of altered GFR in diabetic nephropathy[39]. In the present study, oxidative stress was evaluated by means of tissue MDA, GSH levels and GPx, SOD, CAT and GST activities. The tissue MDA levels were increased, whereas tissue SOD and CAT activities were decreased[35],[40] in group II diabetic nephropathy induced rats. Glucose is oxidized to reactive ketoaldehyde and superoxide radicals. If it is not decomposed by CAT or GPx it causes production of reactive hydroxyl radicals. Excess amounts of free radicals damage cellular proteins and nucleic acids by attaching to them [41]. They cause lipid peroxidation by increasing low-density lipoprotein. Increase in tissue MDA level and decreases in cellular antioxidant enzymes emphasize oxidative stress[42]. We suggest that naringenin

prevent from oxidative stress by reducing lipid peroxidation and increasing GSH levels, SOD and CAT activities[43]. On the other hand, previous experimental studies have shown that GPx enzyme activities reduced in STZ-induced diabetic nephropathy by ant oxidative agents[36,44]. In summary, our data demonstrated that naringenin are beneficial in improving diabetic nephropathy by preventing oxidative stress.

**Table No.1: Shows the levels of serum urea, uric acid, creatinine and protein of control and experimental animals**

| S.No | Particulars (mg/dl) | Group I (Control) | Group II (DN) | Group III (DN+ Naringenin) | Group IV (Naringenin) |
|---|---|---|---|---|---|
| 1 | Urea | 22.65±0.11 | 50.31±0.04[a] | 37.51±0.35[a,b] | 23.10±0.01[b,c] |
| 2 | Uric Acid | 1.23±0.52 | 3.27±0.06[a] | 1.41±0.08[a,b] | 1.31±0.15[b,c] |
| 3 | Creatinine | 0.80±0.12 | 1.56±0.02[a] | 0.58±0.13[a,b] | 0.72±0.04[b,c] |
| 4 | Protein | 10.78±0.02 | 13.59±0.06[a] | 11.45±0.14[a,b] | 9.77±0.03[b,c] |

Values are expressed as mean ± SD for six animals in each group; a - Group I Vs Group II, III and IV, b - Group II Vs Group III and IV; c - Group III Vs Group IV; The significance at the level of $p<0.05$.

**Table No.2: Shows the levels of kidney lipid peroxidation and antioxidants of control and experimental animals**

| S.No | Particulars (mg/dl) | Group I (Control) | Group II (DN) | Group III (DN+ Naringenin) | Group IV (Naringenin) |
|---|---|---|---|---|---|
| 1 | MDA[#] | 0.26±0.03 | 0.65±0.05[a] | 0.42±0.05[a,b] | 0.28±0.01[b,c] |
| 2 | GSH[*] | 5.07±0.53 | 3.28±0.07[a] | 4.45±0.08[a,b] | 4.12±0.16[b,c] |
| 3 | SOD[**] | 6.80±0.13 | 4.50±0.02[a] | 5.53±0.16[a,b] | 5.73±0.05[b,c] |
| 4 | GPx[$] | 1.31±0.02 | 0.59±0.07[a] | 1.15±0.15[a,b] | 1.17±0.04[b,c] |
| 5 | CAT[&] | 51.57±1.20 | 41.70±1.02 [a] | 50.73±1.72 [a,b] | 50.63±1.3 [b,c] |
| 6 | GST [@] | 4.87±0.53 | 3.26±0.15 [a] | 4.08±0.21 [a,b] | 4.06±0.31[b,c] |

[#]nmol of MDA formed/mg protein; [*]µg/mg protein; [**]Units/ mg protein; [$]µmol of reduced GSH oxidized/min/mg protein; [&]µmol of $H_2O_2$ consumed/min/mg protein; [@]nmol of CDNB conjugated/min/mg protein. Values are expressed as mean ± SD for six animals in each group; a - Group I Vs Group II, III and IV, b - Group II Vs Group III and IV; c - Group III Vs Group IV; The significance at the level of $p<0.05$.

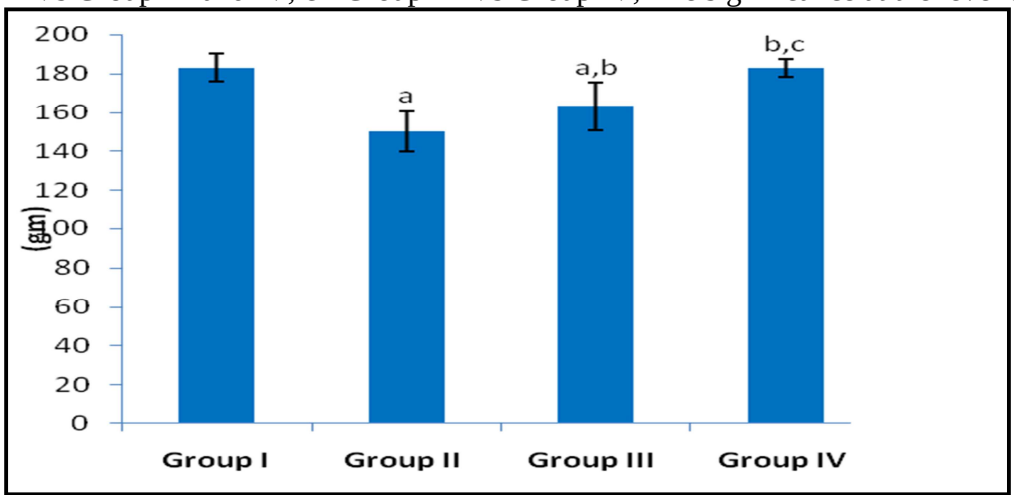


**Figure No.1: Effect of Naringenin on Body Weight of Control and Experimental Animals**

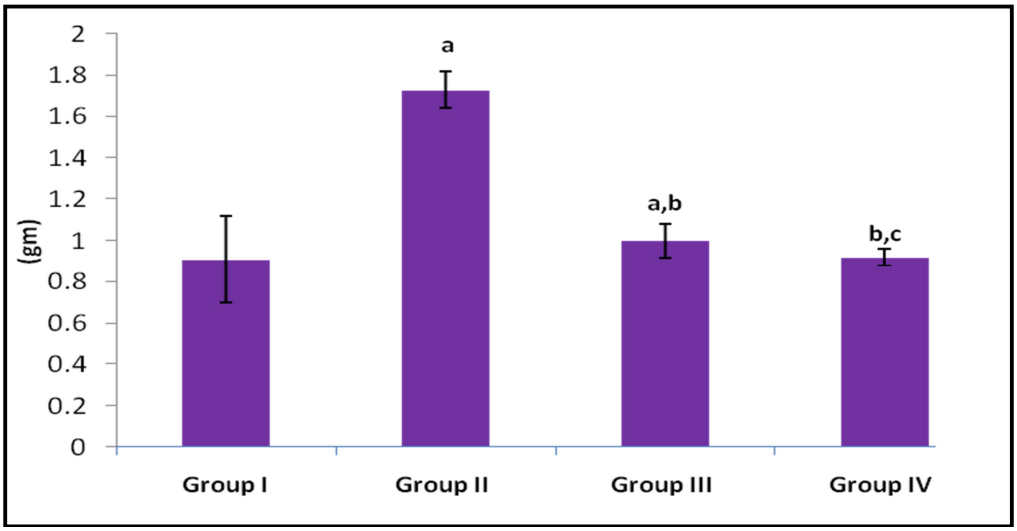


**Figure No.2: Effect of Naringenin on kidney weight of control and experimental animals**

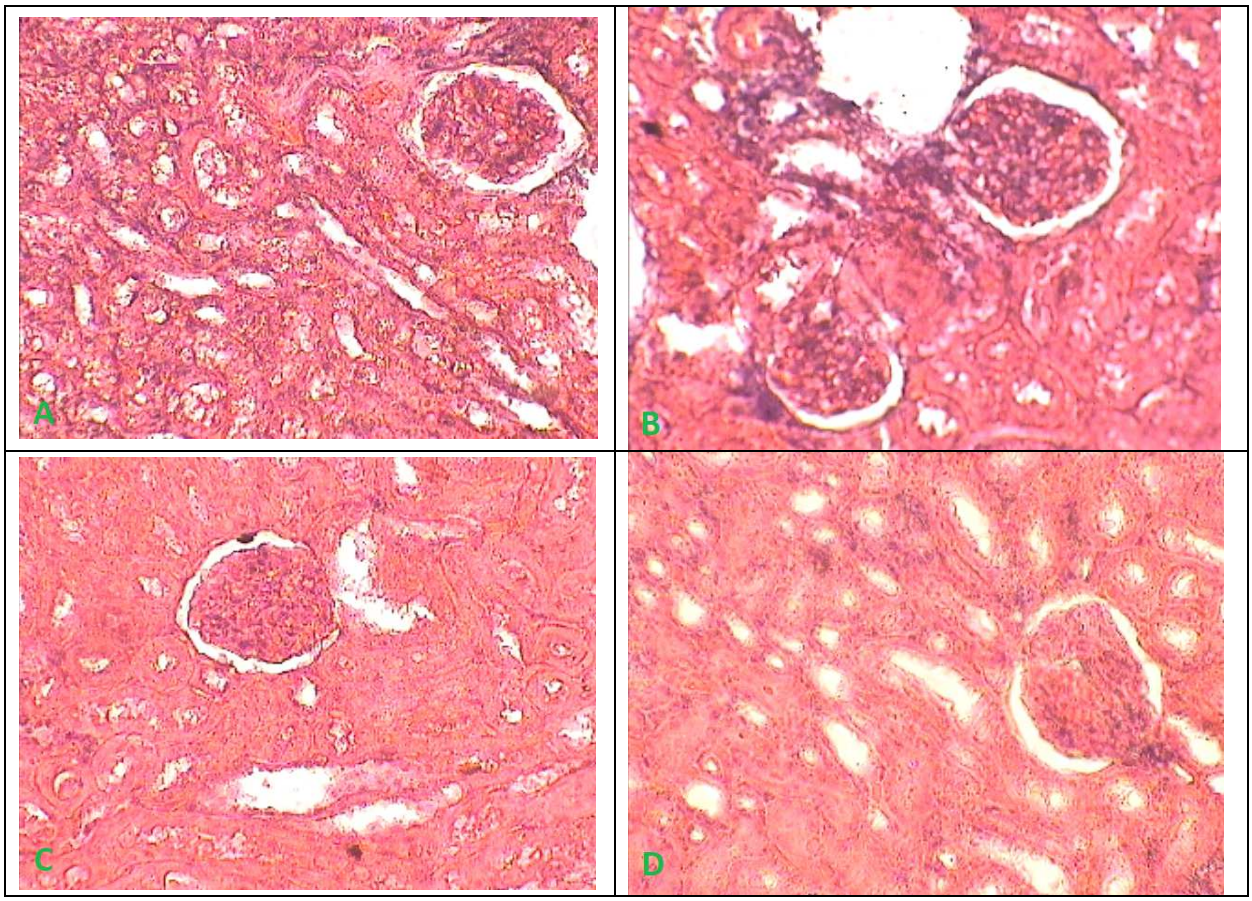


**Figure No.3: Histopathological changes in the kidney tissue of control and experimental groups**

## CONCLUSION

We conclude that naringenin have protective effects against diabetic nephropathy due to its anti-lipid peroxidative effects.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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