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Antidiabetic and nephroprotective activities of *Solanum xanthocarpum* leaves

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ABSTRACT

Diabetes is a metabolic disorder associated with hyperglycemia and caused by defect in insulin secrtion.The aim of the present study was to evaluate the hypoglycemic and nephroprotective activity of Solanum xanthocarpum in alloxan induced diabetic rats. The antidiabetic effect of Solanum xanthocarpum was studied against Alloxan (140mg/k g b.w., i.p.) induced diabetes in wistar rats for doses 250 mg/kg b.w. and 500 mg/kg b.w. (p.o.) for four weeks effect was compared with oral dose of 10mg/kg, b.w. glibenclamide. Diabetes caused by Alloxan treatment increases the level of glucose and biochemical parameter in blood sample but treatment with Solanum xanthocarpum significant decrease the elevated glucose and blood biochemical parameter. Hence, the results obtained in the present study indicate that Solanum xanthocarpum has the potential to treat diabetes mellitus and prevent diabetes mellitus associated renal damage.

Key words: *Solanum xanthocarpum, Glibenclamide, Alloxan, Renal damage, Hypoglycemic and Nephroprotective.*

INTRODUCTION

Diabetes mellitus is a common chronic disease affecting millions of people worldwide. Standard treatment is failing to achieve required correction of blood glucose in many patients. Therefore, there is a need for investigating potential hypoglycemic drugs or herbs to improve glycemic control in diabetic patients [1]. The present number of diabetics worldwide is over 150 million and this is likely to increase to 300 million or more by the year 2025 [2]. Non-insulin-dependent diabetes mellitus or adult-onset diabetes is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [3].

Solanum xanthocarpum (S. xanthocarpum) (family: Solanaceae) commonly known as Yellow Berried Nightshade (syn: Kantakari), is a prickly diffuse bright green perennial herb, woody at the base, 2-3 m height found throughout India, mostly in dry places as a weed on road sides and waste lands. The fruits are of 1.3 cm diameter berry, yellow or white with green veins, surrounded by enlarged calyx [4]. The fruits are known for several traditional medicine uses like anthelmintic, antipyretic, laxative, antiinflammatory, urinary bladder, antiasthmatic, aphrodisiac activities and enlargement of the liver [5]. The stem, flowers and fruits are prescribed for relief in burning sensation in the feet accompanied by vesicular eruptions[6]. The fruits are reported to contain several steroidal alkaloids like solanacarpine, solanacarpidine, solancarpine, solasonine, solamargine and other constituents like caffeic acid, coumarins like aesculetin and aesculin, steroids carpesterol, diosgenin,campesterol, daucosterol and triterpenes like cycloartanol and cycloartenol were reported from the fruits [7]. The antispasmodic, cardiotonic, hypotensive, antianaphylactic, arbuda tumour [8], Anti-urolithiatic and natriuretic activities were also reported [9]. Solasodine is present in a number of Solanum species (Solanaceae) such as Solanum khasianum, Solanum xanthocarpum, Solanum nigrum, Solanumgracile, Solanum laciniatum etc [10]. Lupeol, apigenin and solamergine exhibited Solasodine anticancer property [11], anti-nociceptive [12], antioxidant activities of the chloroform extract[13] and hypoglycaemic [14]. The flavanoids quercitrin and apigenin glycosides are the major chemical constituents which are present in the fruits of S. xanthocarpum [15]. Therefore, present study was designed to demonstrate the antidiabetic and nephroprotective effect of leves extract of of S. xanthocarpum.

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MATERIALS AND METHODS

Preparation of plant extract: 100gram of *Solanum xanthocarpum* leaves was powdered, dried and continuously extracted for 48hrs with ethanol in a Soxhlet apparatus. The collected extract was stored at 0-4°C until used. The plant extract was pooled and evaporated to dry at 60°C.

Preliminary Phytochemical Screening:

Preliminary phytochemical investigation was carried out on ethanolic leaves extract of *Solanum xanthocarpum* for detection of various phytochemicals by following standard methods described in practical Pharmacognosy by C.K. Kokate, and R.K. Khandelwal[16-18].

Acute toxicity:

Rats selected by a random sampling technique were used in the study. Acute oral toxicity was performed as per Organization for Economic Co-operation and Development (OECD) 423 guidelines. Three male Wistar rats weighing between 150-200gm were used for each dose. The dose levels of 5mg, 50mg, 500mg, 1000mg, 2000mg and 3000mg/kg/body weight, per o.s. were selected. The Lethal dose LD-50 value of the extract was determined. The drug was administered orally to rats, which fasted overnight with water ad libitum before the administration of the drug. The body weight of the rat was noted before and after treatment. The animals were observed for toxic symptoms, behavioral changes, locomotion, convulsions and mortality for 72hrs.

Anti-diabetic activity:

Experimental Animals: Alloxan induced diabetic model: [19,20]

Rats were made diabetic by a single intraperitoneal injection of alloxan monohydrate (150mg/kg). Alloxan was first weighed individually for each animal according to the body weight and then solubilized with 0.2 ml saline (154mM NaCl) just prior to injection. Two days after alloxan injection, rats with plasma glucose levels of >140 mg/dl were included in the study. Treatment with plant extracts was started 48 h after alloxan injection.

The various groups used in experiment:

Group I **-** Served as normal control and did not receive any treatment.

Group II **-** Served as diabetic control and received alloxan monohydrate and vehicle

Group III **-** Alloxan + Glibenclamide (10 mg/kg p.o.) served as standard.
Group IV **-** Alloxan monohydrate + ethanolic leaves extract of *Solanum xanthocarpum* 250 mg/kg, p.o.
Group V **-** Alloxan monohydrate + ethanolic leaves extract of *Solanum xanthocarpum* 500mg/kg, p.o.
Treatment Schedule: Total of 30 rats were divided in to 5 groups (n=6) as follows-

Group-I nondiabetic animals: received only 1% gum acacia (1 ml/kg/day, p.o.) for four weeks, and served as control. Group-II to V were rendered diabetic by single intraperitonial dose of alloxan monohyderate 150 mg/kg, in citrate buffer (pH 4.5). Group II received 1 % gum acacia (1 ml/kg/day, p.o.) for four weeks and served as diabetic control. Group-III received glibenclamide (10 mg/kg/day, p.o.) for four weeks. Group-IV and V received two different doses ethanolic leaves extract of *Solanum xanthocarpum*(250 and 500 mg/kg/day, p.o.) for four weeks respectively.

Care of Diabetic Animals: Since diabetic animals drink large amount of fluid and produce large volume of urine, the bedding is changed frequently, usually every day and in some circumstances, more than once per day. Diabetic rats should have sufficient food and water.

Collection blood and serum samples: The blood was drawn from the retro orbital plexus of the rats (fasted for 14 h) under light ether anesthesia on different occasion, i.e., 0, 10th, 20th and 30th day. The blood samples were allowed to clot for 30mins at room temperature and then they were centrifuged at 3000 rpm for 10mins. The resulting upper serum layer was collected in properly labeled, clean and dry micro-centrifuge tubes. The serum samples were stored at -400 C and analyzed either immediately or within two weeks.The parameters studied were as follows: Biochemical parameters such as

a. Serum total cholesterol.
b. Serum and creatinine.
c. Serum urea.
d. Serum and Urine total protein.

- Body weight of an animal.
- Histopathological studies of kidney.

Statistical Analysis:
Results were expressed as mean ± SEM, (n=6). Statistical analyses were performed with one way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test by using Graph Pad Instat Software. P value less than 0.05 was considered to be statistically significant. *P<0.05, **<0.01 and ***<0.001, when compared with control and toxicant group as applicable.

RESULTS

Preliminary phytochemical screening:
Results of the preliminary phytochemical investigation on ethanolic leaves extract of *Solanum xanthocarpum* leaves are shown the presence of Alkaloids, Carbohydrates, Flavonoids, Saponins, Steroids, Glycosides etc.

Acute Toxicity:
No acute toxicity was observed for ethanol extract of *Solanum xanthocarpum* when it was administered orally at high dose level (3 g/kg body weight), which is higher than effective antihyperglycemic dose, and closely observed for 24 hrs for any mortality and next 10 days for any delayed toxic effects on gross behavioral activities.

Anti-diabetic study of *Solanum xanthocarpum* in alloxan induced diabetic rats:
a) Body weight:
The Diabetic control showed significant decrease in the body weight during the treatment period. The diabetic animals treated with ethanolic leaves extract of *Solanum xanthocarpum* (250mg/kg) showed slight reduction in body weight but not much when compared to control. The group that received ethanolic leaves extract of *Solanum xanthocarpum* 500mg/kg had shown significant results(Table 1 and Fig 1).

Table No. 1: Effect of *Solanum xanthocarpum* on body weight in alloxan induced diabetic rats

Groups	Body weight of the animal (gms)			
	Initial	10th day	20th day	30th day
Normal	166±3.15	168±6.32	179±2.26	**188±4.42**
Alloxan+vehicle	178±2.44	169±3.46	154±2.30	**145±1.60**
Alloxan+Glibenclamide 10mg/kg	160±3.60	158±6.32	166±4.24**	**170±1.28***
Alloxan+ *Solanum xanthocarpum* 250mg/kg	169±2.20	167±3.72*	158±2.42*	**156±8.26***
Alloxan+ *Solanum xanthocarpum* 500mg/kg	**168±8.52**	**157±6.64****	**162±8.24****	**166±4.22****

Values are Mean ±S.E.M; n=6; ns= non-significant, *P <0.05, **P < 0.01 and ***P<0.001 vs. Diabetic Control

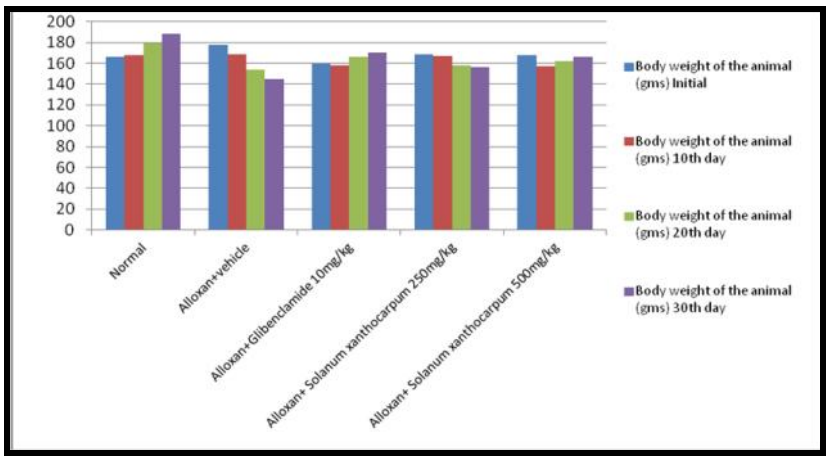


Fig. 1: Effect of *Solanum xanthocarpum* on body weight in alloxan induced diabetic rats

b) Biochemical parameters:
Diabetic animals treated with *Solanum xanthocarpum* showed significant decrease in serum creatinine , serum cholesterol and urea, and significant increase in serum albumin and total protein when compared with diabetic control (Table 2 and Fig. 2-5).

Table No. 2: Effect of *Solanum xanthocarpum* on biochemical parameters in alloxan induced diabetic rats.

Groups	Serum protein (mg/dl)	Serum urea (mg/dl)	Serum creatinine	Serum cholesterol
Normal	6.9±0.4	37.4±0.2	0.74±0.01	**71.22±4.6**
Alloxan+vehicle	4.4±0.2	82.6±4.2	1.7±0.02	**132.36±4.2**
Alloxan+Glibenclamide10mg/kg	6.8±0.2**	39.4±2.6**	0.78±0.08***	**73.28±2.4*** **
Alloxan+ *Solanum xanthocarpum* 250mg/kg	5.4±4.2	55.6±6.8**	1.22±0.02**	**99.92±2.6****
Alloxan+ *Solanum xanthocarpum* 500mg/kg	**6.5±0.6****	**42.3±0.3****	**0.82±0.06*** **	**76.22±4.8*** **

Values are Mean ± S.E.M; n=6 * P<0.05, **P < 0.01 and ***P < 0.001 vs. Diabetic Control

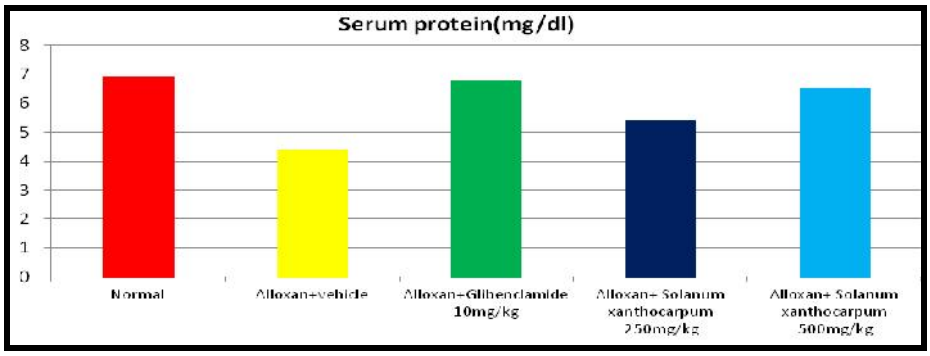


Fig. 2: Effect of *Solanum xanthocarpum* on Serum Protien in alloxan induced diabetic rats

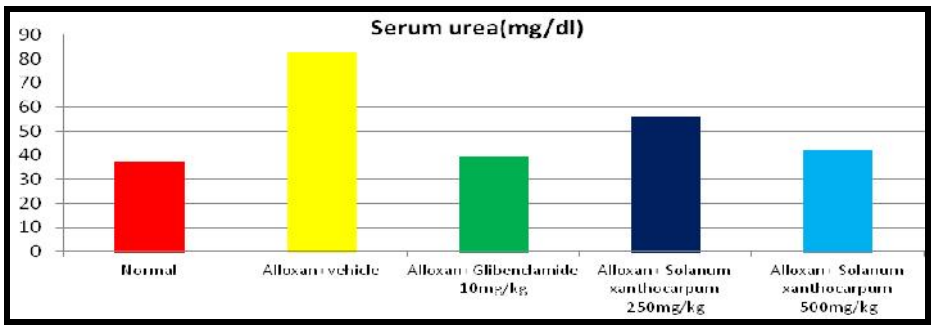


Fig. 3: Effect of *Solanum xanthocarpum* on Serum Urea in alloxan induced diabetic rats

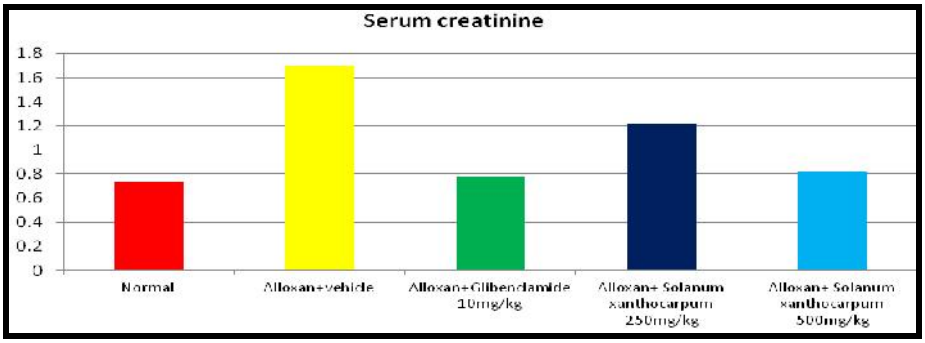


Fig. 4: Effect of *Solanum xanthocarpum* on Serum Creatinine in alloxan induced diabetic rats

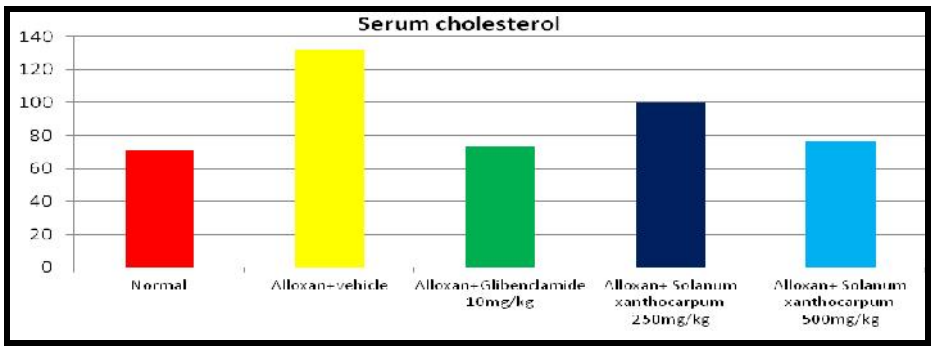
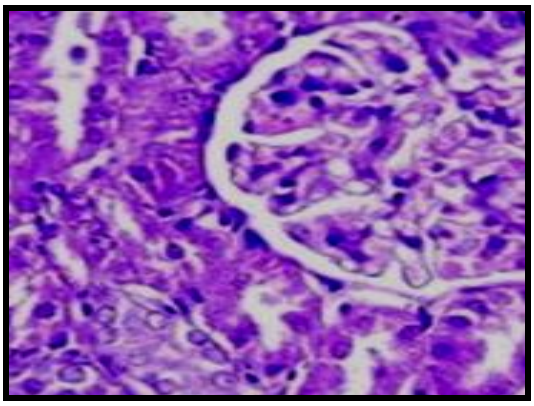


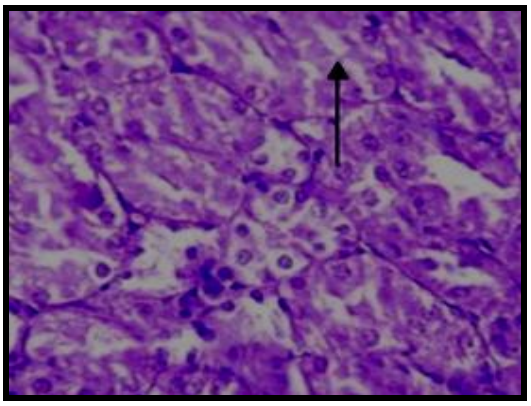
Fig. 5: Effect of *Solanum xanthocarpum* on Serum Cholesterol in alloxan induced diabetic rats

Effect of *Solanum xanthocarpum* on histopathology of kidney:

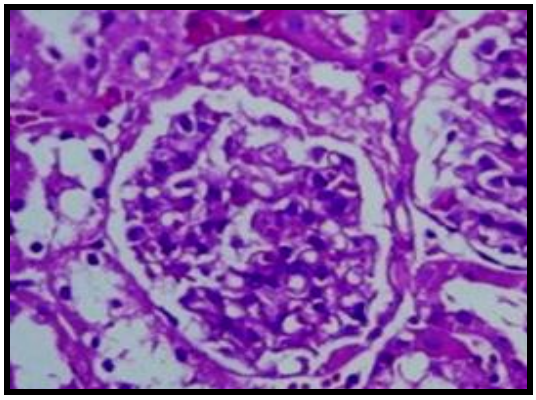
In present study, histopathology of control group showed normal structure of glomerulus, while diabetic control group showed significant mark of glomerulosclerosis and hyalinization which occurs because of severe diabetic condition (diabetic nephropathy). Diabetic group treated with *Solanum xanthocarpum* 500mg/kg, p.o. showed absence of the sclerotic lesions produced by diabetic condition. While Glibenclamide treated diabetic groups showed no necrosis, as near to the normal condition. Diabetic group treated with *Solanum xanthocarpum* 250mg/kg, p.o. show mild necrosis of kidney produced by diabetic condition (Fig. 6).



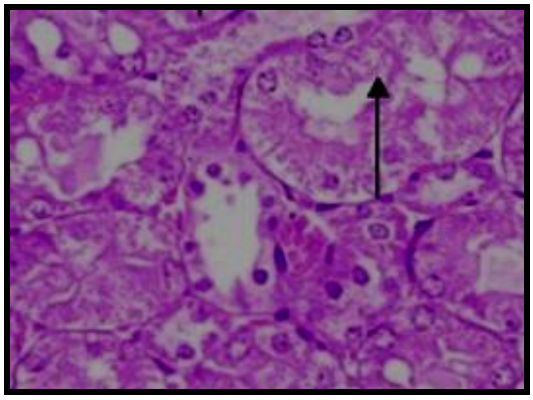
a) Control kidney(Group I) showing normal structure of glomerulus



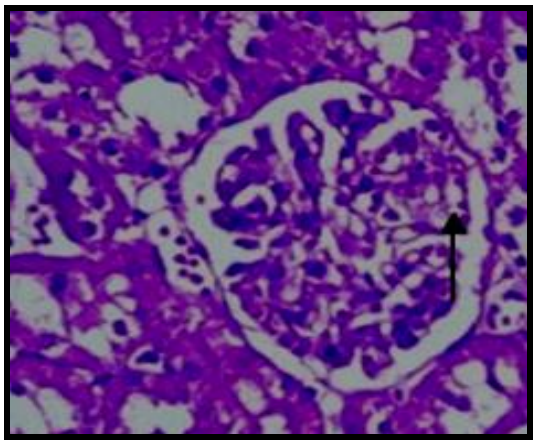
b) Diabetic group kidney(Group II) showing significant mark of nephritis



C) Group III(shows no nephritis)



D) Group III(shows mild nephritis)



E) Group V(shows very mild nephritis)

Fig. 6: Effect of *Solanum xanthocarpum* on histopathological studies of kidney in alloxan-induced diabetic rats

DISCUSSION

Diabetes mellitus ranks highly among the top ten disorders which cause mortality throughout the world. Diabetes mellitus being chronic disorder, treatment without side effect for long term control is important. Present antidiabetic agent possess side effect as risk of hypoglycemia, anemia, choestatic jaundice [21]. There has been growing public interest in herbal medication for treatment of diabetes.

In the present study the periodic estimation of plasma glucose revealed that ethanolic leaves extract of *Solanum xanthocarpum* produced significant antihyperglycemic activity which began from 20nd day of treatment and it progressed throughout the study. The antidiabetic effect of the *Solanum xanthocarpum* could possibly be due to presence of glycosides, terpenoids, tannins and saponins. Substances like glycosides, alkaloids, terpenoids, tannins and saponins are frequently implicated as having antidiabetic effects [22].

It is reported that the recovery in body weight is far less in the poorly controlled diabetic rats as compared to well-controlled diabetic rats. Various reports suggest that there is reduction in the body weight in diabetic rats. Loss of body weight could be due to, dehydration and catabolism of fats and protein seen during diabetes mellitus [23]. In the present study diabetic control group rats showed significant loss of body weight. All animals treated with *Solanum xanthocarpum* showed significant prevention of the loss in body weight throughout the study. This prevention of loss in body weight by *Solanum xanthocarpum* may be due to increasing glucose uptake in peripheral tissues or inhibiting catabolism of fat and protein or by glycemic control.

Diabetes produces qualitative and quantitative changes in the composition of the basement membrane and this altered material undergoes accelerated glycosylation and further rearrangement to form advanced glycation end-products (AGEs), which stimulate protein synthesis, further decrease degradability of the basement membrane, increase its permeability and cause endothelial dysfunction. Hyperglycemia increases the expression of transforming growth factor beta (TGFβ) in the glomeruli and of matrix protein specifically stimulated by cytokine. TGFβ may contribute to both the cellular hypertrophy and enhanced collagen synthesis is observed in diabetic nephropathy [24].

During diabetes, there is increased protein catabolism with inflow of amino acids to liver, which feed gluconeogenesis and accelerate ureagenesis, resulting in hypoproteinemia and hypoalbuminemia [25]. Diabetic hyperglycemia induces elevation of the levels of serum creatinine, urine total protein and urine albumin which are considered as significant markers of renal dysfunction [26].

In the present study, diabetic animals treated *Solanum xanthocarpum* showed reduction in proteinurea and albuminurea and also showed improvement in the serum total protein and albumin level. Treatment with *Solanum xanthocarpum* also prevented the rise in serum creatinine levels. These results indicate that *Solanum xanthocarpum* attenuates the progression of renal damage in alloxan induced diabetic rats. The use of typical antioxidants alone or in combination may retard or even prevent the normal progression of diabetic complications [27].

In case of uncontrolled diabetes there is accumulation of lipids in kidney. Excessive production and accumulation of lipids can have devastating effect on renal structure and function [28]. Changes in the fractions of the lipid in renal cortex and medulla readily show its abnormality in diabetes [29]. In the present study it was found that concentrations of total lipids were significantly increased in cortical and medullary region of the kidney; concentration of total cholesterol was significantly increased in cortical region. *Solanum xanthocarpum* treated diabetic rats showed significant reduction in the total cholesterol and triglyceride level in the kidney homogenate. The glycemic control exerted by *Solanum xanthocarpum* may have affected the dislipidemia and the subsequent accumulation of the lipids in the kidney.

The histopathological study of diabetic control group showed significant mark of glomerulosclerosis and hyalinization which was probably due to severe diabetic condition (diabetic nephropathy); and the diabetic groups treated with *Solanum xanthocarpum* showed absence of the sclerotic lesions produced by diabetic condition indicating the protective effect of *Solanum xanthocarpum* on the kidneys of the diabetic animals.

Hence, the results obtained in the present study indicate that ethanolic leaves extract of Solanum xanthocarpum-graecum has the potential to treat diabetes mellitus and prevent diabetes mellitus associated renal damage.

CONCLUSION

In the present study the ethanolic leaves extract of *Solanum xanthocarpum-graecum* shown better Anti-diabetic and Nephroprotective activities in experimental rat models, it may be due to the presence of alkaloids, flavonoids and other poly phenolic compounds. Hence, the research justifies that the leaves extract can be effectively used in treatment of diabetes as well as nephrotoxicity. Further studies are needed to isolate and characterize the active component (s) responsible for the anti-diabetic and nephroprotective properties of the test extract and findings should be confirmed by performing clinical studies.

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