

# The antidiabetic effect of leaf and stem extract of *Crossandra infundibuliformis* in alloxan-induced diabetic rats and diabetic nephropathy in male rats

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## Abstract

**Background:** The prevalence of diabetes is growing in the world's population. The epidemic of disease is rising in the population of India and other countries. Many herbal plants are in use for the management of diabetes till today. They are being advantageous with the lesser side effects and high therapeutic potential than the standard antidiabetic drugs. **Materials and Methods:** The present research is to investigate the antidiabetic activity and antioxidant effect of ethanolic extract of *Crossandra infundibuliformis* leaves and stems (ECILS) in alloxan-induced diabetic rats. Diabetes is induced in the experimental animals by the administration of alloxan (150 mg/kg *i.p.*) for a week. The total treatment period was about 30 days. Blood glucose levels were tested using standard blood glucometer. This activity also includes the estimation of biochemical parameters and *in vivo* antioxidant parameters such as lipid peroxidation, reduced glutathione, and catalase. Histopathological studies were performed on liver and kidney. **Results:** The diabetic + ECILS rats experienced a significant reduction in glucose, total cholesterol, triglycerides, and increase in high-density lipoproteins compared to disease control. **Conclusion:** These results demonstrate that *C. infundibuliformis* possess antidiabetic activity, potent antioxidant activity, and can be used in future studies for the estimation of distinct phytochemicals with the antidiabetic activity.

**Key words:** Alloxan, antidiabetic activity, antioxidant studies, *Crossandra infundibuliformis*, diabetic nephropathy, histopathology

## INTRODUCTION

Diabetes mellitus is a disease, in which homeostasis of carbohydrate, protein, and lipid metabolism is improperly regulated by hormone insulin resulting in elevation of fasting and postprandial blood glucose levels.<sup>[1]</sup> The major chronic complications associated with diabetes include retinopathy, neuropathy, nephropathy, and atherosclerotic coronary artery disease and peripheral atherosclerotic vascular disease.<sup>[2]</sup> According to recent estimation, the global population is approaching the midst of a diabetes pandemic. By the year 2020, the total number people suffering from diabetes is predicted to reach 3.7 million.<sup>[3]</sup> Besides hyperglycemia, several other factors such as hyperlipidemia and enhanced oxidative stress play a major role in diabetic pathogenesis.

Despite the great strides that have been made in the understanding and management of this disease, the graph of diabetes-related mortality is rising unabated. Although a number of synthetic drugs are available in the market diabetes and its related complications still remain uncontrolled. On the other hand, traditional medicinal plants have been used successfully since ancient times by physicians and laymen to treat diabetes and its related complications, presenting a stirring prospect for the expansion of an alternative way of

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treatment of diabetes.<sup>[4,5]</sup> Herbal drugs are prescribed widely, even when their biologically active compounds are unknown, due to their effectiveness, lesser side effects, and relatively low cost.<sup>[6,7]</sup>

*Crossandra infundibuliformis* (Acanthaceae) is an enduring herb local to India and Sri Lanka and other Asian nations and it is ordinarily developed as a blooming plant, it is the evergreen sub bush with polished and wavy margined leaves and fan-molded blossoms which may show up whenever consistently.<sup>[8]</sup> This bloom hue run from the regular orange shading to a salmon-orange coral to the red shading and even green turquoise. These plant parts are utilized since old time in treating different sorts of turmoil like aggravation and it is likewise known for its injury mending action. This plant is additionally notable for its sexual enhancer action and for its mitigating movement, it is otherwise called sparkler since when the dried case of the plant interacts with water it tears open as a sparkler, subsequently, these plants were granted with this name.<sup>[9,2]</sup> The present investigation is directed to the exploration of the antidiabetic activity of the ethanol extract of leaves and stems of *C. infundibuliformis*. An attempt was also made to find out antioxidant potential of the aforementioned plant with an aim to establish a correlation with the reduction of oxidative state associated with diabetes.<sup>[10-14]</sup>

## MATERIALS AND METHODS

### Procurement and Authentication of Plant

The leaves and stems of *C. infundibuliformis* were collected from Guntur, Andhra Pradesh. The plant material was identified and authenticated by Dr. P. V. Prasanna, Plant Taxologist, Scientist F and HOD Professor, Ministry of Environment, Botanical Survey of India, Hyderabad, Telangana.

### Preparation of Plants Extract

The leaves and stems of *C. infundibuliformis* were collected and washed thoroughly with distilled water to make sure the leaves and stems are free of dust and are shade dried. The dried leaves and stems are then powdered finely using mechanical grinder. And then, required quantity of the powder is subjected to solvent extraction with ethanol. The obtained extract is dried completely using desiccators.<sup>[15-18]</sup>

### Animals and Treatment

#### Animals

Healthy male Sprague Dawley rats weighing between 250 g and 300 g were procured and maintained in polypropylene cages at ambient temperature of  $22 \pm 1^\circ\text{C}$  and relative humidity of 50–60% with a 12 h light/dark cycle in registered

animal house. The animal experiments were carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals approved under the number (1048/a/07/CPCSEA), India, and approved by the Institutional Animal Ethics Committee. Throughout the experimental period, the animals were fed with standard pellet diet and water *ad libitum*.

One week after treatment, rats with moderate diabetes having glycosuria (indicated by Benedict's qualitative test) and hyperglycemia (i.e., with a blood glucose level above 150 mg/dl) were used for the experiment.

Before the experiment, rats were fasted for about 12 h and were divided into five groups ( $n = 6$ ).

- Group 1 Normal control rats received physiological saline (200 mg/kg) intragastrically for 30 days.
- Group 2 Diabetic control rats received physiological saline and single dose alloxan (150 mg/kg *i. p*)
- Group 3 Alloxan-induced diabetic rats received Gliclazide for 30 days (25 mg/kg *p. o*).
- Group 4 Alloxan-induced diabetic rats received an ethanolic extract of *C. infundibuliformis* leaves and stems ECIS for 30 days (200 mg/kg *p. o*).
- Group 5 Alloxan-induced diabetic rats received ECILS for 30 days (400 mg/kg *p. o*).

The blood glucose level was estimated by enzymatic glucose oxidase method using a commercial one touch glucometer (Accu-Chek) before treatment (T0), 2 h (T2h), and 1, 2, 3, and 4 weeks (T1w, T2w, T3w, and T4w) after administration of extracts. Blood was withdrawn from the tail vein each time.

All groups received the above treatments for 30 days.

### Biochemical Parameters

Serum collected on respective days is used for the estimation of different biochemical parameters such as glucose, High Density Lipoprotein (HDL), Total cholesterol, Total Protein,

**Table 1: Preclinical phytochemical screening**

Name of phytochemical constituent	Ethanolic extract
Carbohydrates	+
Amino acids	+
Proteins	+
Alkaloids	+
Cardiac glycosides	+
Saponins	+
Phytosterols	–
Steroids	+
Flavonoids	+
Phenols and tannins	+

Albumin, Serum Glutamic Pyruvic Transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase (SGOT), Bilirubin, and Triglycerides.<sup>[19]</sup>

### In Vivo Antioxidant Parameters

5-5-dithiobis(2-nitrobenzoic acid) reagent was used to estimate reduced glutathione (GSH) levels in tissue homogenates and the absorbance was read at 412 nm. The amount of GSH in the sample was calculated in microgram per ml from a standard curve obtained and represented in GSH per total tissue protein. Evaluation of kidney homogenate for lipid peroxidation levels and Catalase (CAT) activities was carried out.<sup>[20]</sup>

### Histopathology of Liver and Kidney

At the end of treatment, animals were sacrificed by the spinal cord dislocation technique, and liver was isolated immediately.

The isolated liver and kidney are stored in 10% formalin solution for the histopathology studies. For the study of the effect of ECILS on liver and kidney, tissue slides are prepared and stained using simple stain technique and observed under light microscope.

The organ is homogenized at 4°C for 1 min and centrifuged at 14,000 RPM at 4°C for 15 min; the supernatant is collected and used for the *in vivo* antioxidant studies.<sup>[21]</sup>

### Statistical Analysis

The results were expressed as mean ± SEM (standard error of the mean [SEM]). Statistical analysis was calculated using one-way Analysis of Variance (ANOVA) followed by *post hoc* Dunnett's test for multiple comparisons and statistical significance was set at  $P < 0.05$ . Values are represented as mean ± SEM; a (\*\*\*) –  $P < 0.0001$ , b (\*\*) –  $P < 0.01$ , and c (\*) –  $P < 0.05$ .

## RESULTS

### Preliminary Phytochemical Screening

The percentage yield of the ECILS was about 96.04%. The phytoconstituents present in the plant are found to be tannins, glycosides, flavonoids, phenolic compounds, amino acids, and alkaloids. The results are summarized in Table 1.

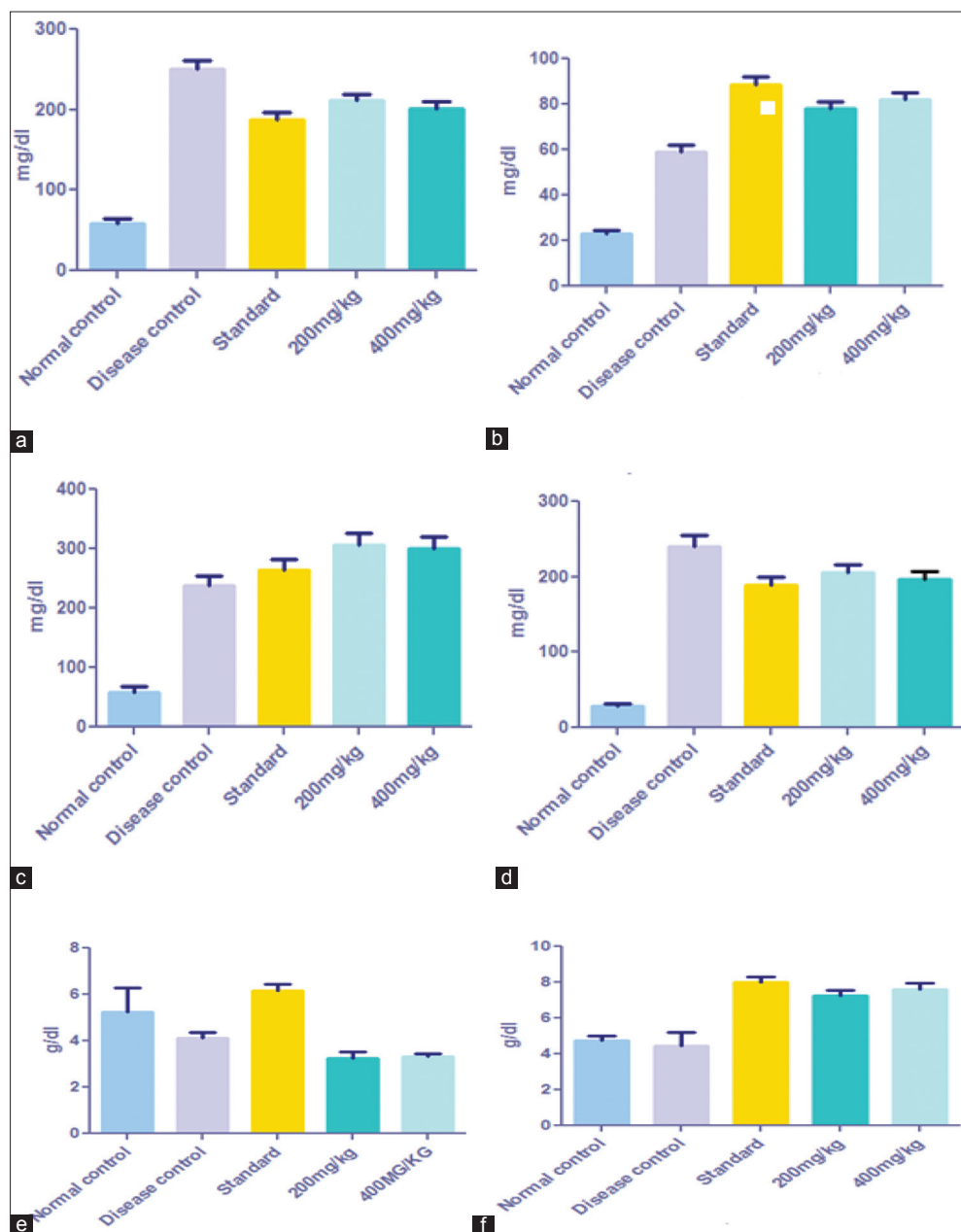
### Effect of ECILS on Serum Parameters and Lipid Profile

The estimated values of biochemical parameters in all the experimental rats during the treatment period are summarized in Table 2 and Figure 1.

Table 2: Effect of ECILS on serum parameters and lipid profile in alloxan-induced diabetic rats

Days	Glucose levels	HDL levels	Total cholesterol	Triglycerides	Albumin	Total protein	Direct bilirubin	Total bilirubin	SGOT	SGPT
Groups										
Normal control	59.15±5.86	23.31±1.11	58.72±8.94	28.42±3.76	5.235±1.07	4.74±0.26	0.343±0.05	0.483±0.09	23.37±4.26	21.18±4.68
Disease control	250.5±11.11	59.10±3.21	238.5±16.41	240.2±15.29	4.147±0.22	4.468±0.75	5.817±0.62	1.70±0.08	218.7±9.24	154.3±11.33
Standard	188.2±8.25 <sup>a</sup>	78.28±2.75 <sup>a</sup>	264.1±18.61 <sup>ns</sup>	189.0±10.16 <sup>b</sup>	6.160±0.27 <sup>c</sup>	8.02±0.25 <sup>a</sup>	4.04±0.59 <sup>ns</sup>	2.720±0.18 <sup>b</sup>	131.7±7.31 <sup>a</sup>	197.2±7.05 <sup>c</sup>
ECILS 200 mg/kg	211.1±8.0 <sup>b</sup>	82.26±2.80 <sup>a</sup>	306.6±20.27 <sup>c</sup>	205.5±10.44 <sup>ns</sup>	3.23±0.30 <sup>ns</sup>	7.272±0.29 <sup>a</sup>	5.59±0.47 <sup>ns</sup>	3.043±0.24 <sup>a</sup>	105.5±10.94 <sup>a</sup>	92.03±9.04 <sup>a</sup>
ECILS 400 mg/kg	202.00±7.70 <sup>b</sup>	88.79±3.20 <sup>a</sup>	299.7±20.59 <sup>ns</sup>	197.2±9.80 <sup>c</sup>	3.31±0.13 <sup>ns</sup>	7.607±0.34 <sup>a</sup>	4.588±0.51 <sup>ns</sup>	2.907±0.25 <sup>a</sup>	109.8±7.72 <sup>a</sup>	162.8±12.40 <sup>ns</sup>

SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase, HDL: High-density lipoprotein, ECILS: Ethanolic extract of *Crossandra infundibuliformis* leaves and stems



**Figure 1:** Graphs representing the effect of the ethanolic extract of *Crossandra infundibuliformis* leaves and stems (ECILS) on serum parameters and lipid profile in Alloxan-induced diabetic rats. (a) Effect of ECILS on blood glucose levels, (b) effect of ECILS on high-density lipoprotein levels, (c) effect of ECILS on total cholesterol, (d) effect of ECILS on triglyceride levels, (e) effect of ECILS on albumin, (f) effect of ECILS on total protein, (g) effect of ECILS on direct bilirubin levels, (h) effect of ECILS on total bilirubin levels, (i) effect of ECILS on serum glutamic oxaloacetic transaminase levels, (j) effect of ECILS on serum glutamic pyruvic transaminase levels

### Estimation of *In Vivo* Antioxidant Studies

The *in vivo* parameters such as lipid peroxidation, reduced GSH, and CAT were estimated in experimental rats and are summarized in Table 3.

The significant values are mentioned in Table 3 and Figure 2, and the levels of lipid peroxidation have significantly increased in disease control group and significantly decreased in standard and ECILS-treated groups. The levels of CAT have been significantly decreased in disease control group, and

moderate increased values are seen in standard and ECILS-treated groups.

In disease control group, significant decreased values of reduced GSH are observed and significantly increased values are seen in standard and ECILS-treated groups.

### Histopathology of Liver Tissue

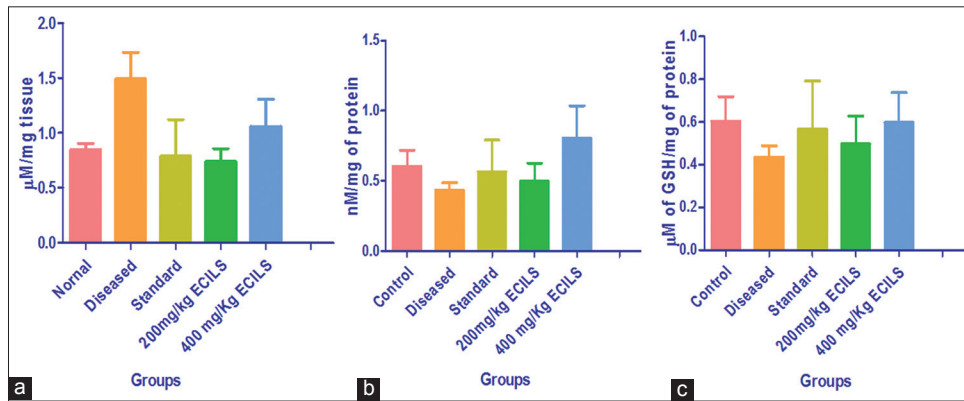
Non-diabetic rats have shown normal structure of the liver tissue. In diabetic control rats, the organ is seen

with inflammation and tissue damage. In standard and extract-treated groups, liver is seen with mild lobular inflammation and the tissue recovery is seen which is shown in the figures. Figure 3 shows the photographs of the liver tissue which represents the effect of the plant extract.

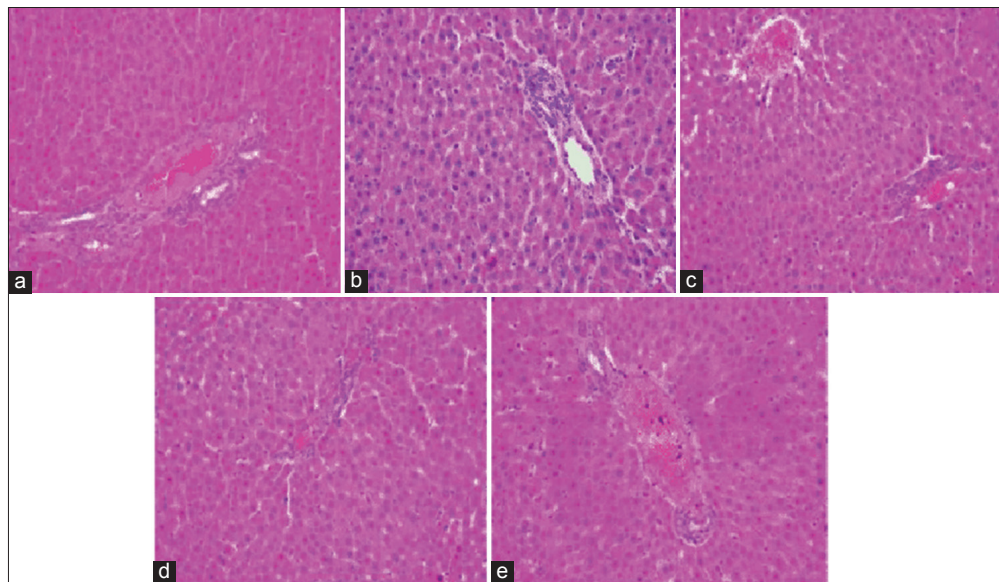
### Histopathology of Kidney

Kidney of the control rats shows normal renal histological structure of renal parenchyma and glomeruli, as shown in

Figure 4a. Figure 4b shows kidney of rat from the disease control group with degeneration in most of the glomeruli with wide urinary space and lobulation. Vacuolar degeneration in some tubular epithelial cells was observed. Treating diabetic rats with standard drug nearly restored the renal tissues to their normal histology with no histopathological changes, as shown in Figure 4c. In Figure 4d and e, kidney tissue of diabetic rats treated with ECILS, most renal tubules and glomerulus appeared normal. Dose-dependent improvement can be observed.



**Figure 2:** Graphs representing the effect of the ethanolic extract of *Crossandra infundibuliformis* leaves and stems on *in vivo* antioxidant parameters in various groups; (a) lipid peroxidation, (b) catalase, and (c) reduced glutathione

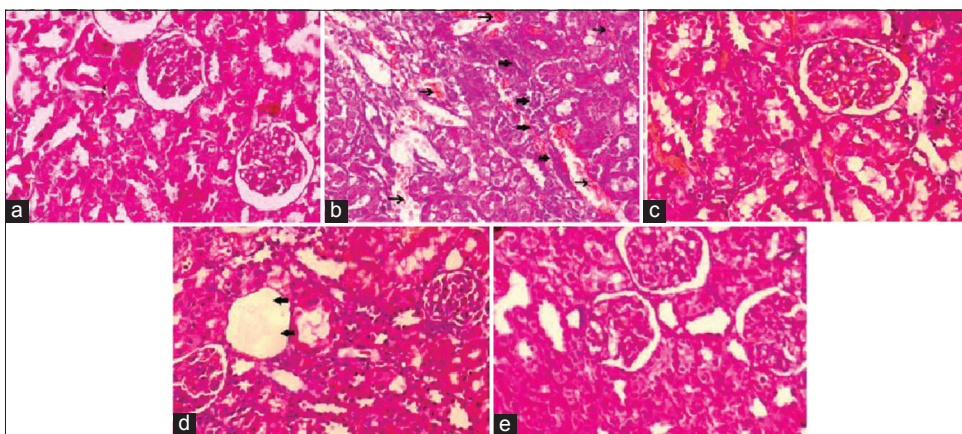


**Figure 3:** Photomicrographs of histopathological studies of liver tissue, (a) normal group, (b) disease control, (c) standard group, (d) ethanolic extract of *Crossandra infundibuliformis* leaves and stems (ECILS) (200 mg/kg), (e) ECILS (400 mg/kg)

**Table 3:** Effect of ECILS on *In vivo* antioxidant parameters in Alloxan-induced diabetic rats

Groups	Normal group	Disease control	Standard	ECILS 200 mg/kg	ECILS 400 mg/kg
Parameters					
Lipid peroxidation	0.554 ± 0.02	1.594 ± 0.24	0.674 ± 0.04 <sup>a</sup>	0.754 ± 0.02 <sup>a</sup>	0.692 ± 0.05 <sup>a</sup>
Reduced glutathione	8.403 ± 0.23	0.889 ± 0.15	3.320 ± 0.24 <sup>c</sup>	1.216 ± 0.49 <sup>ns</sup>	1.533 ± 0.46 <sup>ns</sup>
Catalase	1.326 ± 0.16	0.273 ± 0.65	0.844 ± 0.05 <sup>a</sup>	0.673 ± 0.06 <sup>c</sup>	0.732 ± 0.01 <sup>b</sup>

ECILS: Ethanolic extract of *Crossandra infundibuliformis* leaves and stems



**Figure 4:** Photomicrographs of histopathological studies of kidney; (a) normal group, (b) disease control, (c) standard group, (d) ethanolic extract of *Crossandra infundibuliformis* leaves and stems (ECILS) (200 mg/kg), (e) ECILS (400 mg/kg)

## DISCUSSION

Alloxan, a beta-cytotoxin, destroys  $\beta$ -cells of islets of Langerhans of pancreas, resulting on endogenous insulin secretion and paves the ways for the decreased utilization of glucose by the tissue.<sup>[22]</sup> It results in elevation of blood glucose level. Expression of elevated fasting blood glucose level confirmed the induction of diabetes in alloxan-induced experimental rats. The experiment focused on exploring the competence of ethanolic extract of leaves and stems of *C. infundibuliformis* for the correction of diabetes to substantiate folklore claim. The differences between the initial and final fasting blood glucose levels of different groups in both short-term and long-term studies exposed a significant elevation in blood glucose level in diabetic controls as compared with that of normal, extract-treated, and gliclazide-treated animals. Maintenance of blood glucose level with extract-treated rats vindicates the effectiveness of the extract in experimental diabetic animals.

The extract exhibited a significant control of serum lipid profiles in diabetic rats. Diabetes is associated with hyperlipidemia.<sup>[23]</sup> It is well known that insulin activates enzyme lipoprotein lipase, which hydrolyzes triglyceride under normal conditions. Destruction of beta-cells leads to the depletion of plasma insulin, which results in hyperlipidemia. The significant control of plasma lipid levels suggests that the extract may produce its action by improving insulin secretion.

Excessive hepatic glycogenolysis and gluconeogenesis associated with decreased utilization of glucose by tissue are the fundamental mechanism underlying hyperglycemia in diabetic state.<sup>[24]</sup> Aberration of liver glycogen synthesis or glycogenolysis in diabetes may be due to lack of or resistance to insulin, which is essential to activate glycogen synthase system. The significant increase of liver glycogen level in extract-treated diabetic groups may be due to reactivation of the glycogen synthase system by

improving insulin secretion. Diabetes is associated with weight loss.<sup>[25]</sup> The reversal of weight loss in extract-treated diabetic group indicates that the restorative effect of the extract may be by the reversal of gluconeogenesis and glycogenolysis.

Experimental results also reflect that the extract is capable of reducing the oxidative state associated with diabetes. The reduction of reduced Glutathione (GSH) levels in tissues in the extract-treated diabetic group ensures the antioxidant potential of the extract. Alloxan produces diabetes by liberating oxygen-free radicals, which cause lipid peroxide-mediated pancreatic injury.<sup>[26,27]</sup> The extract may scavenge free radicals and facilitate the reconstruction of pancreatic cells to release more insulin and ultimately produces an antidiabetic effect.

The results of this investigation revealed that *Crossandra infundibuliformis* possesses significant antidiabetic activity in alloxan-induced diabetes.

## CONCLUSIONS

In our study, we have found that ECILS decreases blood glucose in Alloxan diabetic rats. Mechanism of the action of extracts in reducing the diabetic is not known. In fact, it was found that traditional medicines used in human diabetes also have a significant antioxidant activity. It may be possible that these extracts may reduce the effect of free radicals release during diabetes which may be one of the causative agents for the tissue distraction and insulin resistance. Treatment with antioxidants and scavengers of reactive oxygen species inhibits the development of complications and tissue damage in diabetic patients and experimental animals.

In conclusion, the results of the present study show that the extract brings back the blood glucose levels to normal in diabetes-induced rats, i.e., shows hypoglycemic activity.

In near future, flavonoids, tannins, and saponins, which are the principal phytochemicals of the extract, might be the building block for new diabetes treatments.

The present studies indicated a significant antidiabetic and renoprotective effects with the ethanolic extract of *C. infundibuliformis* and supported its traditional usage in the control of diabetes and its complications.

### Current and Future Developments

At present, many medicinal plants used for the treatment of diabetes mellitus do not have side effects.

Treatment development for diabetes mellitus needs to be investigated in the human subject for confirmation of these results. Future research should focus on human subject treatment with medicinal plants to eliminate complications of the chemical medicine drugs.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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