ANTI HYPERGLYCAEMIC AND ANTI-OXIDANT ACTIVITY OF *CATUNAREGAM SPINOZA* (THUNB) AGAINST DEXAMETHASONE INDUCED DIABETES IN RATS

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**ABSTRACT**

**Objective:** The study was aimed at evaluating the folkloric use of the *Catunaregam spinosa* (Thunb) bark for its hypoglycaemic and antioxidant activity against dexamethasone-induced diabetes in wistar rats.

**Methods:** Diabetes was induced in wistar rats by dexamethasone administration 10 mg/kg, b. wt., s. c. f or 11 consecutive days to all group animals (except Group I). After confirmation of diabetes, the animals were divided into 5 groups (n=6). Group I: Vehicle control treated with normal saline only, Group II: Diabetic control treated with dexamethasone only, Group III: Standard control treated with dexamethasone plus glibenclamide (5 mg/kg, b. wt., p. o). Group IV and V: Test control received dexamethasone plus ethanolic extract of *Catunaregam spinosa* (EECS) at graded doses of 200 mg/kg, b. wt. and 400 mg/kg, b. wt. p. o for 21 days respectively. On the last day of the experiment, the effect of *Catunaregam spinosa* bark was measured by estimating the biochemical and antioxidant parameters.

**Results:** There was a significant alteration in the serum glucose, HbA1c, total proteins, serum lipid profile and tissue antioxidant parameters in dexamethasone-treated animals when compared to the normal control rats.

In test groups treated with glibenclamide and EECS, it was significantly ameliorated the altered parameters such as serum glucose, Hba1c, total proteins, serum lipid profile and the antioxidant parameters like SOD, CAT, GSH and MDA when compared to dexamethasone-treated animals with evidence of histopathological studies of the pancreas.

**Conclusion:** The results indicated that the ethanolic extract of *Catunaregam Spinosa* (Thunb) bark has shown the hypoglycaemic and antioxidant property.

**Keywords:** Natural products, *Catunaregam spinosa* (Thunb), Hypoglycaemic and Antioxidant activity, Dexamethasone

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**INTRODUCTION**

Diabetes mellitus is a metabolic disorder characterized by an abnormality in carbohydrate, lipid and protein metabolism resulting in chronic hyperglycemia and abnormality of lipid profile. Chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and eventually the failure of organs, especially the eyes, kidneys, nerves, heart and blood vessels [1]. Environmental factors such as diet, obesity, sedentary lifestyle and other factors like high family aggregation, insulin resistance, nutritional status, age increase the risk of diabetes [2]. Diabetes is managed with drugs such as metformin, sulfonylureas, thiazolidinedione’s etc and as well as artificial insulin [3, 4]. The serious adverse side effects like liver problems, lactic acidosis and diarrhoea [5, 6]. Diabetes is currently affecting around 143 million people [7], the number of those affected is increasing day by day by 2030 and it is predicted to reach 366 million populations worldwide [8]. Management of diabetes without any side effects is still a challenge for the medical system. This leads to an increasing search for improved anti-diabetic drugs [9].

Medicinal plants have been used in the Indian traditional system of medicine and have shown anti-diabetic activity [10, 11]. The number of active constituents present in medicinal plants is thought to act on a variety of targets by different mechanisms. *Catunaregam spinosa* (Thunb) belongs to the family Rubiaceae is commonly known as Gedhpal or Emetic nut. This species is common as undergrowth in the sub-Himalayan tract [12]. The raw-fruits have a highly astringent taste due to high tannin content. The seeds contain essential oil and organic acid. The dried and powdered fruit pulp is credited with astringent and carminative property.

The plant bark is reported for diarrhoea, dysentery, abortifacient, anthelmintic and antipyretic [14]. It is also considered to be a sedative, hypoglycaemic and stomach ache as first aid remedy. Roots are used in the treatment of epilepsy, eye ache and urinary infection. The fruit is used as emetic and the leaves are used in pulmonary infections [15, 16]. *Catunaregam spinosa* also used as carminative, antipyretic, cures abscess, ulcers, inflammations, wounds, tumours and skin diseases [17]. Based on the scientific evidence of the data, the research was carried out to evaluate the hypoglycaemic and antioxidant activity of ethanolic extract of *Catunaregam spinosa* (Thunb) (EECS) bark against dexamethasone-induced diabetes in wistar rats.

**MATERIALS AND METHODS**

**Collection and authentication of plant specimen**

The stem bark s of *Catunaregam spinosa* (Thunb) were collected from surrounding areas of Seshachalam hills, Chittoor district and Andhra Pradesh (A. P). The plant material was authenticated by Dr. K. Madhava chetty, Professor, Department of Botany, Sri Venkateswara University, Tirupati, A. P, and India.

**Animals**

Healthy Adult Male Wistar rats weighing 150-200 gms were procured from Raghavendra enterprises, Bangalore and were maintained under standardized environmental conditions 12-h light/dark cycle, 24 °C and 35 to 60% humidity, provided free access to pellet diet and purified drinking water ad libitum. The experimental protocol was approved by Institutional Animal Ethical Committee of Krishna Teja Pharmacy College, Tirupati, A. P (Registered No. 1521/P0/11/CPCEA-Committee for the purpose of control and supervision of experimental animals).

**Preparation of plant extract**

The plant barks were isolated, washed, shade dried and mechanically grinded to coarse powder. The powdered drug was...
subjected to continuous hot percolation with solvent 70% ethanol using soxhlet apparatus with 1:4 volumes. The extraction was carried out until the solvent becomes colourless and the solvent was removed from the extract by evaporation. The dried extract thus obtained was preserved in desicator [18]. The EECS was evaluated for phytochemical constituents using standard procedures [19, 20].

**Experimental design**

Experimental rats were taken and divided into five groups each containing six animals.

- **Group I** animals served as vehicle control received 0.5 ml of normal saline orally.
- **Group II** animals served as diabetic control received dexamethasone (10 mg/kg, b. wt., s. c) for 11 consecutive days [21].
- **Group III** animals served as standard control received dexamethasone (10 mg/kg, b. wt., s. c) for 11 days and glibenclamide (5 mg/kg, b. wt., p. o) for 21 days.
- **Group IV and V** animals served as test control received dexamethasone (10 mg/kg, b. wt., s. c) for 11 d and EECS at graded doses of 200 mg/kg b. wt, and 400 mg/kg b. wt., p. o for 21 days respectively.

**Assessment of the hypoglycemic effect**

The blood samples were collected through retro-orbital route from each rat under mild ether anesthesia on 22nd day and serum was separated by centrifugation of blood at 4000 rpm for 10 min. The serum was used for the estimation biochemical parameters such as Glycosylated haemoglobin (HbA1c), serum glucose levels, Total cholesterol (TC), Triglycerides (TGL), High density lipoprotein (HDL), Low density lipoprotein (LDL), Very low density lipoprotein (VLDL) [22-26] and total protein (TP) [27]. From each group, one animal was taken and sacrificed for pancreas isolation and same one part is used for estimation of antioxidant parameters like Superoxide dismutase (SOD), Catalase (CAT), Glutathione reductase (GSH) and Malondialdehyde (MDA) [28-31] and another part processed for Histopathological studies [32].

**Statistical analysis**

The results were expressed as mean±SEM/SD differences in groups for biochemical estimations. Statistical analysis was determined by one way-analysis of variance (ANOVA), individual groups were compared using Dunnet’s t-test. P value<0.05 has been considered as a statistical significance level.

**RESULTS**

Preliminary phytochemical screening of EECS revealed the presence of Carbohydrates, Glycosides, Saponins, Terpenoids, Phenols, Tannins, Flavonoids, Proteins, Amino acids and Phytosterols.

**Acute toxicity studies and test dose selection**

The acute toxicity studies were conducted as per OECD (Organization for economic co-operation and development) 423 guidelines (Acute Toxic Class Method). No sign of toxicity and mortality was observed up to the maximum dose administered a dose of 2000 mg/kg, b. wt. p. o of EECS. The dose was selected based on the maximum dose administered with 1/10th and 1/20th as low dose and a high dose of test extract.

**Effect of EECS on HbA1c and serum total protein**

Table 1 represents a significant (P<0.001) increased in the level of glycosylated haemoglobin (HbA1c) and decreased in the serum total protein levels upon administration of dexamethasone as compared to the vehicle-treated animals. Upon treatment with standard drug glibenclamide (5 mg/kg, b. wt., p. o) and EECS at both dose levels (200 mg/kg, b. wt, and 400 mg/kg, b. wt., p. o) for 21 d showed a significant (P<0.05) (P<0.01) restoration of the abnormal levels compared to the diabetic control rats.

| Groups               | Glycosylated Haemoglobin-HbA1c (%) | Total protein (mg/dl) |
|----------------------|-----------------------------------|-----------------------|
| Vehicle control      | 5.22±0.661                        | 6.780±0.947           |
| Diabetic control     | 8.58±0.568                        | 4.600±0.687           |
| Standard control     | 5.14±0.683***                     | 6.260±0.596***        |
| EECS-I (200 mg/kg, b. wt.) | 5.80±0.624***                  | 4.924±0.778***        |
| EECS-II (400 mg/kg, b. wt.) | 5.70±0.870***                  | 5.960±0.969***        |

Values were expressed as mean±SEM (n=6). *P<0.05, **P<0.01, ***P<0.001. As compared with diabetic control (One-way ANOVA followed by Dunnett’s test).

**Effect of EECS on serum glucose levels**

Table 2 shows dexamethasone administration raised the serum glucose levels significantly (P<0.001) on day 4, 7, 10, 15 and 21 leading to hyperglycemia when compared to the vehicle control animals. Reversal of raise in serum glucose level was found in the animals treated with standard drug glibenclamide (5 mg/kg, b. wt, p. o) and EECS at both dose levels (200 mg/kg, b. wt, and 400 mg/kg, b. wt., p. o) for 21 d when compared to the diabetic control rats.

| Groups               | Serum Glucose Levels (mg/dl) |
|----------------------|-----------------------------|
|                      | 4th day                      | 7th day                      | 10th day                     | 15th day                     | 21th day                     |
| Vehicle control      | 85.0±3.536                  | 88.0±2.550                  | 89.2±1.772                   | 91.0±2.646                   | 97.3±1.333                   |
| Diabetic control     | 159.2±2.933                 | 197.4±2.098                 | 210.0±2.450                  | 217.0±1.453                  | 219.6±2.881                  |
| Standard control     | 103.4±1.715***              | 99.8±1.020***               | 94.8±1.655***                | 92.6±1.333***                | 88.6±2.881***                |
| EECS-I (200 mg/kg, b. wt.) | 127.6±1.094***              | 121.0±1.049***              | 110.4±1.679***               | 108.3±1.332***               | 105.6±1.373***               |
| EECS-II (400 mg/kg, b. wt.) | 110.4±1.852***              | 105.4±2.821***              | 103.4±2.513***               | 97.0±1.577***                | 94.6±0.967***                |

Values were expressed as meanSEM (n=6). *P<0.05, **P<0.01, ***P<0.001. As compared with diabetic control (One-way ANOVA followed by Dunnett’s test).

**Effect of EECS on serum lipid profile**

Table 3 demonstrates that dexamethasone for 11 consecutive days causes an imbalance in lipid metabolism provokes hyperlipidemic condition in rats with significant (P<0.001) elevation of TC, TGL, LDL, VLDL and decrease in the HDL levels when compared to the vehicle control rats. Treatment with standard drug glibenclamide (5 mg/kg, b. wt., p. o) and EECS at both dose levels (200 mg/kg, b. wt, and 400 mg/kg, b. wt., p. o) for 21 d showed a significant (P<0.05) (P<0.01) amelioration of abnormal lipid profile when compared to the diabetic control rats.
### Table 3: Effect of EECS on serum lipid profile in dexamethasone-induced diabetic rats

| Groups                  | Serum lipid profile (mg/dl) | Total cholesterol | Triglycerides | HDL | LDL | VLDL |
|-------------------------|-----------------------------|-------------------|--------------|-----|-----|------|
| Vehicle control         |                             | 181.8±5.936       | 146.2±2.663  | 44.0±1.703 | 41.00±1.316 | 11.60±1.509 |
| Diabetic control        |                             | 265.8±10.220      | 177.2±2.728  | 23.6±1.80  | 93.20±3.737 | 33.60±1.034 |
| Standard control        |                             | 190.8±3.388**     | 148.6±2.064**| 22.2±2.969**| 52.80±2.374**| 12.60±0.924**|
| EECS-I (200 mg/kg, b.wt.)|                             | 213.0±4.477*      | 161.0±3.894* | 37.2±2.489*| 67.00±2.447**| 19.20±0.884**|
| EECS-II (400 mg/kg, b.wt.)|                          | 195.4±3.749**     | 154.0±2.140**| 40.0±2.316**| 57.20±2.374**| 14.80±0.374**|

Values were expressed as mean±SEM (n=6). *P<0.05, **P<0.01, ***P<0.001. As compared with diabetic control (One-way ANOVA followed by Dunnett’s test)

### Effect of EECS on tissue pro-oxidant and anti-oxidants

Table 4 demonstrates that dexamethasone induction caused significant (P<0.001) decrease in the antioxidant enzymes like SOD, CAT, GSH and increase in the LPO levels indicating that production of reactive oxygen species leading to free radical damage when compared to the vehicle control rats. Treatment with standard drug glibenclamide (5 mg/kg, b.wt., p.o) and EECS at both dose levels (200 mg/kg, b.wt., and 400 mg/kg, b.wt., p.o) for 21 d showed a significant (P<0.05) (P<0.01) reversal of abnormal pro-oxidant and antioxidant enzymes when compared to the diabetic control rats.

### Table 4: Effect of EECS on tissue pro-oxidant and anti-oxidants in dexamethasone-induced diabetic rats

| Groups                  | SOD (μg/mg protein) | Catalase (μM H₂O₂ consumed/mg protein) | GSH (μg of GSH/mg protein) | LPO (nM of MDA/mg protein) |
|-------------------------|---------------------|---------------------------------------|---------------------------|----------------------------|
| Vehicle control         | 18.20±1.583         | 32.00±0.816                           | 29.40±0.509               | 45.80±2.374                |
| Diabetic control        | 8.680±1.080         | 22.80±0.874                           | 12.40±0.509               | 91.60±2.509                |
| Standard control        | 16.00±1.316***      | 31.00±0.812***                        | 27.30±0.633***            | 49.40±1.280***             |
| EECS-I (200 mg/kg, b.wt.)| 13.40±1.509’       | 28.80±0.972’                          | 24.60±0.599’              | 65.00±2.362’               |
| EECS-II (400 mg/kg, b.wt.)| 15.00±1.312**      | 30.40±0.949**                         | 26.60±0.897**             | 54.00±1.312**              |

Values were expressed as mean±SEM (n=6). *P<0.05, **P<0.01, ***P<0.001 as compared with diabetic control (One-way ANOVA followed by Dunnett’s test)
Glibenclamide and EECS 200 mg/kg and 400 mg/kg b. wt., haemoglobin [43]. The rate of glycation is proportional to the concentration of blood glucose [44, 45]. Treatment with glibenclamide and EECS 200 mg/kg and 400 mg/kg b. wt., p.o. ameliorated the abnormal levels of HbA1c and TP when compared to the diabetic control rats depicted in table 1.

In the present study, it has been found that the elevation of serum glucose and abnormal changes in the lipid profile in dexamethasone-treated rats indicating that the hyperglycemia and Hyperlipidemia [46, 47]. Dexamethasone increases in glucose levels leading to hyperglycemia due to the inhibition of GLUT-4 (glucose transporter) translocation from intracellular compartments to the plasma membrane particularly of skeletal muscles [48, 49]. The elevation of serum glucose levels in diabetic control rats were significantly restored upon treatment with the standard glibenclamide and ethanolic extract of Catunaregam spinosa (Thunb) at both dose levels (200 mg/kg, b. wt., and 400 mg/kg, b. wt., p. o.) for 21 d as compared to the vehicle control rats which was depicted in table 2. The possible mechanism by which EECS mediated its anti-hyperglycemic effect could be by the potentiation of pancreatic secretion of insulin from existing β-cells of islets thereby increase glucose utilization from tissues through GLUT-4.

Pharmacological doses of glucocorticoids induce ob gene expression in rat adipocyte tissues within 24 h which is followed by complex metabolic changes like hyperleptinemia, resulting in decreased in food consumption, with enhanced blood glucose and an imbalance in lipid metabolism leading to Hyperlipidemia [50-53]. The administration of dexamethasone, significantly (P<0.001) elevate the serum lipid parameters such as TC, TGL, LDL, VLDL and decrease in the HDL levels when compared to the vehicle control rats. Treatment with EECS (200 mg/kg, b. wt., and 400 mg/kg, b. wt., p. o.) for 21 d had ameliorated the abnormal lipid profile depicted in table 3. From the results of the present study, it may be suggesting that the lipid improvement in food intake and HDL levels and also a reduction in blood glucose. And it confirms that EECS shows protection of vital organs like pancreas, liver, heart, spleen and kidney thereby reducing the causation of diabetes [52].

Histopathological studies
Dexamethasone administration for 21 d revealed that the pancreas with degeneration of pancreatic cells and inflammation vacuoles may be due to the free radical damage compared to the normal vehicle control with normal parenchymatous cell without any degeneration and inflammation. Treatment with glibenclamide and EECS significantly reduced the marked inflammation and degeneration of pancreas as compared to the diabetic control rats.

DISCUSSION
In the present study Catunaregam spinosa (Thunb) was selected for hypoglycaemic and antioxidant activity evaluation owing to its ethnomedicinal use in curing diabetes. Therefore, the study was undertaken to justify its claimed use. Ethanolic extract of Catunaregam spinosa (Thunb) (EECS) bark was prepared by Soxhlet method and stored in the refrigerator at 4 °C. Rats were selected as experimental animals for evaluating anti-hyperglycaemic and antioxidant activity. Acute toxicity was conducted as per OECD guidelines and the EECS was not showed any toxicity at the dose of 2000 mg/kg and no death was reported for 72h. Preliminary phytochemical screening of EECS revealed the presence of Carbohydrates, Glycosides, Saponins, Terpenoids, Phenols, Tannins, Flavonoids, Proteins, Amino acids and Phytosterols.

Subcutaneous administration of dexamethasone for 11 d causes significant (P<0.001) elevation of HbA1c and decrease in the serum total protein levels in diabetic control rats as compared to the vehicle control. Glucocorticoids are widely used therapeutic tools particularly in treatment for anti-inflammatory and immune-modulatory purposes. Side effects of glucocorticoid treatment include steroid diabetes [33, 34]. It induces hyperglycemia is partially due to increased hepatic glucose production and insulin resistance of peripheral tissues. Moreover, glucocorticoids are known to inhibit insulin secretion [35, 36]. The underlying mechanism involves increased α2-adrenoceptor signaling [37], increased Kv channel activity [38] and impaired glucose metabolism [39, 40]. They diminish glucose utilization in the peripheral tissues cause an increase in protein breakdown by increasing the synthesis of glutamine and lipolysis, thereby providing amino acids and glycerol for gluconeogenesis [41]. HbA1c as a biomarker for monitoring the levels of glucose among type 2 diabetic patients provides a reliable measure of chronic glycaemia and correlates well with the risk of long-term diabetes complications. So it is currently considered the test of choice for monitoring and chronic management of diabetes [42]. During diabetes, the excess of glucose present in the blood reacts with hemoglobin to form glycosylated haemoglobin [43]. The rate of glycation is proportional to the concentration of blood glucose [44, 45]. Treatment with glibenclamide and EECS 200 mg/kg and 400 mg/kg b. wt., p.o. significantly reduced the marked inflammation and degeneration of pancreas as compared to the diabetic control rats.
CONCLUSION

Medicinal plants have continued to be a powerful source for new drugs contributing about 90% of the newly discovered pharmaceuticals. As for the developed countries, the use of herbal medicine for chronic diseases is encouraged because there is concern about the adverse effects of chemical drugs and treatment using medicines of natural origin appears to offer more gentle means of managing such diseases. Herbal drugs are prescribed widely because of their effectiveness, fewer side effects and are relatively low in cost. The above data suggest that the ethanolic extract of Catunaregam spinosa (Thunb) bark possess hypoglycemic and antioxidant activity in dexamethasone-treated rats as evidenced by the restoration of the abnormal parameter levels. This may be due to the presence of bioactive constituents in the plant such as tannins, flavonoids, saponins, polyphenols etc. Further studies are required to isolate the active principle responsible for hypoglycemic and antioxidant activity.

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ABBREVIATIONS

A: P: Andhra Pradesh, CPSEA: Committee for the purpose of control and supervision of experimental animals, ANOVA: Analysis of variance, LPO: Lipid peroxidation, OECD: Organization for economic co-operation and development, TP: Total protein, HbA1c: Glycosylated haemoglobin, GLUT-4: Glucose transporter 4, VLDL: Very low density lipoproteins, LDL: Low density lipoproteins, TGL: Triglycerides, TC: Total cholesterol, HDL: High Density Lipoproteins, Cu/Zn: Copper/Zinc, GST: Glutathione-S-transferase, GPx: Glutathione peroxidise, TNF-α: Tumour necrosis factor-α, IL-8: Interleukins-8, H2O2: Hydrogen peroxide, SOD: Superoxide dismutase, CAT: Catalase, GSH: Reduced Gluthione, MDA: Malondialdehyde, EECs: Ethanolic extract of Catunaregam spinosa, AC: Acinar cells, EX: Exocrine, IL: Islets of langerhans, NC: Necrotic changes, DC: Degenerative changes, C: Congestion

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest

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