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A Study on Antidiabetic Potential of Dried Fruits Extract of Eucalyptus Globulus in Experimental Animals

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Abstract: The study investigated the antidiabetic potential of an ethanolic fruit extract of Eucalyptus globulus (EG) using male Albino Wistar rats. Diabetes was induced in the rats using Alloxan, and EG was administered orally at different doses (100, 200, and 400mg/kg/day). Glibenclamide was used as a standard drug for comparison. The rats' blood glucose levels and body weight were measured at the beginning and end of the 14-day treatment period. The study also evaluated hypoglycemic effects, oral glucose tolerance, and biochemical parameters associated with diabetes. Histopathological examination of the pancreas was performed to assess any regenerative effects. The results showed that the oral administration of EG significantly reduced blood glucose levels, demonstrated hypoglycemic potential, improved oral glucose tolerance, and increased body weight compared to the toxic control group. Biochemical parameters associated with diabetes also improved with EG treatment. Additionally, histopathological examination revealed that the ethanolic extract of EG helped in the regeneration of pancreatic tissue previously damaged by Alloxan. The findings suggest that the ethanolic fruit extract of EG, which contains bioactive polyphenols like Ellagitannins, has promising antidiabetic properties and merits further investigation in clinical studies and potential drug development.

Keywords: Antidiabetic potential, Eucalyptus globulus, Alloxan, Insulin, alloxan.

1. Introduction

Diabetes mellitus (DM) is the chronic metabolic & pancreatic islet disorder mainly characterized by disruption in carbohydrates, protein, and fat metabolism caused by an inability to produce insulin or a defect in utilization. The hyperglycemia caused due to decreased insulin production is called Type-1 diabetes and hyperglycemia due insufficient insulin utilization is called Type-2 diabetes (1). The feature of diabetes mellitus is polyuria, polydipsia, weight gain and polyphagia. It is also characterized by chronic hyperglycemia and glucosuria, caused by an absolute or relative deficiency of insulin. This may result into the development of further complications which include hypertension, atherosclerosis, ketosis, gangrene and microcirculatory disorders. It is also associated with long-term complications

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including retinopathy, nephropathy, neuropathy and angiopathy [2,3]. The IDF (International Diabetes federation) has subsequently released estimates of the numbers of people with diabetes for 2003 and forecasts for 2025 of 194 million and 334 million, respectively. India leads the world with largest number of diabetic subjects earning of term "diabetes capital of the world" [4]. Hyperglycemia can be handed initially with oral synthetic 2 Advances in Pharmacological Sciences agent and insulin therapy. Glucose lowering drugs usually succeed in lowering blood sugar levels, therapeutic agents like Insulin, Sulfonylureas, Meglitinides, Biguanides, Thiozolidinediones, DPP-4 inhibitors, α-Glucosidase Inhibitors, Incretin agonists, D2 Agonist may reduce the risk of type 2 diabetes but healthy lifestyle choices remain essential [5,6]. However, on chronic usage most of these agents produced several side effects including hypoglycemic coma, insulin resistance, hyper- sensitivity, jaundice, abdominal pain, anorexia and metallic taste. Because of the high mortality and morbidity arising from its attendant complications and problems associated with the use of conventional antidiabetic agents[7,8]. In the natural system of medicine, many plants have been claimed to be useful for the treatment of diabetes mellitus. The dependence of large rural population on medicinal plants for treatment of diabetes is because of its availability and affordability (9,10). The current worldwide trends towards utilization of plant-derived natural remedies have, therefore, created a dire need for accurate and up-to-date information on the properties, uses, efficacy, safety, quality & less cost of medicinal plant products than the semi- synthetics or synthetics. The plant kingdom has become a target for the search by multinational drug and biologically active lead compounds. In this regard herbal, ayurvedic remedies can improve diabetic conditions without side effects (11-13). Ellagitannins (ETs) and ellagic acid (EA) are polyphenols present in some fruits, nuts and seeds, such as pomegranates, black raspberries, raspberries, strawberries, walnuts, almonds & also present in EG. Ellagitannins contain various numbers of hexahydroxydiphenoyl units, as well as galloyl units and/or sanguisorboyl units bounded to sugar moiety. In order to determine the quantity of every individual unit, the hydrolysis of the extracts with trifluoroacetic acid in methanol/water system is performed. They form a diverse group of bioactive polyphenols with anti-inflammatory, anticancer, antioxidant and antimicrobial (antibacterial, antifungal and antiviral) activity (14-,17). So, the present study was undertaken to Evaluate Antidiabetic Potential of EG plant Extract using Alloxan - induced Diabetic Rats.

2. Materials & Methods

2.1 Collection of Plant Material

The *Eucalyptus globulus* (EG) fruits were carefully collected from the local area and subjected to authentication by a renowned botanist. A voucher specimen was prepared and preserved for future reference, ensuring the accuracy and reliability of the plant material used in the study.

2.2 Preparation of ethanolic Extract:

The fruits of Eucalyptus globulus (EG) were collected and subjected to shade drying for a week after thorough cleaning. Subsequently, the dried fruits were coarsely ground to prepare the ethanolic fruit extract using a Soxhlet apparatus. The obtained extract was concentrated to dryness using a rotary evaporator under reduced pressure and low temperature (<40°C). To preserve its potency, the extract was stored in an air-tight container at 4°C for future studies.

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2.3 Phytochemical Screening:
The ethanolic fruit extract of *Eucalyptus globulus* (EG) underwent phytochemical analysis to determine the presence of various compounds. The analysis aimed to identify the existence of volatile oils, carbohydrates, alkaloids, glycosides, polyphenols, flavonoids, tannins, propanoids, sterols, terpenoids, ketones, and alcohols in the extract.

2.4 Experimental Animals
Male Albino Wistar rats weighing between 150-200g were chosen as subjects for the experimental study. The animals were housed in an animal facility approved by the Institutional Animal Ethics Committee (IAEC-CPCSEA) and maintained under standard laboratory conditions. The laboratory environment was set at a temperature of 22 ± 2°C, relative humidity of 50 ± 15%, and a 12-hour light/dark cycle. Throughout the study, the rats had unrestricted access to standard pellets as their food and water was provided *ad libitum.*

2.5 Induction of Diabetes:
To induce diabetes in the male Albino Wistar rats, a single ip injection of Alloxan monohydrate was administered in a 0.9% NaCl solution over 5 minutes, given at a dose of 150mg/kg/day for three consecutive days. After 72 hours of Alloxan administration, rats with moderate diabetes, exhibiting glycosuria and hyperglycemia (i.e., with a blood glucose level of 200-300mg/dl), were selected for the experiment (18).

2.6 Collection of Blood Samples, Blood Glucose & Body Weight Determination:
Blood samples were collected from the tail tip of the rats for analysis. Fasting blood glucose levels and body weight measurements were taken on both the initial and final days of the study. Blood glucose estimation was performed using a one-touch ACCU-CHECK Active Glucometer, utilizing glucose test strips. On the final day of the study, blood samples were obtained from the retro-orbital plexus of overnight fasted rats under mild ether anesthesia, and fasting blood sugar was estimated. Subsequently, the body weight of the animals was recorded for analysis (19).

2.7 Biochemical Estimation:
Blood samples were collected to estimate the levels of blood glucose, serum insulin, and lipid profile components (total cholesterol, triglycerides, HDL, LDL, VLDL) in the serum. After completing the respective treatments, the animals were euthanized using a high dose of anesthesia, and histopathological studies were conducted.

2.8 Experimental Design

2.8.1 Acute Toxicity Study
An acute toxicity study was conducted on the ethanolic fruit extract of Eucalyptus globulus (EG) following OECD guidelines no. 423. Healthy male Albino Wistar rats were randomly divided into four groups, with three animals in each group. The rats were fasted overnight, only provided with water. The ethanolic fruit extract of EG was orally administered to the rats using increasing doses (100, 500, 1000, and 2000mg/kg/day) via an intra-gastric tube, employing the up and down method to determine safe doses. The animals were continuously observed for 1 hour and then frequently monitored for 4 hours up to the end of 24 hours (20)

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2.8.2 Hypoglycemic Evaluation

Animals were divided into four groups of six animals in each group. Animals were kept fasted overnight (14hrs.) before treatment.
Group I- (Control) rats received vehicle -5% Tween 80 (10 ml/kg/day p.o.).
Group II- Received ethanolic fruit extract of EG (EFEG) (100mg/kg/day p.o.) Low Dose
Group III- Received ethanolic fruit extract of EG (EFEG) (200mg/kg/day p.o.) Medium Dose
Group IV- Received ethanolic fruit extract of EG (EFEG) (400mg/kg/day p.o.) High Dose
Blood glucose was estimated on 0, 1, 2, 3 & 4^{th} day of the treatment.

2.8.3 Oral Glucose Tolerance Test (OTGT)

For OGTT evaluation, Male Albino Wistar Rats were used and divided into five groups of six animals in each group. Animals were kept fasted overnight (14hrs.) before treatment.
Group I- (Control) rats received vehicle that was D- Glucose (2gm/kg p.o.).
Group II- (Standard) rats received Glibenclamide (0.5mg/kg i.p.).
Group III- Received ethanolic fruit extract of EG (EFEG) (100mg/kg/day p.o.) (Low)
Group IV- Received ethanolic fruit extract of EG (EFEG) (200mg/kg/day p.o.) (Medium)
Group V- Received ethanolic fruit extract of EG (EFEG) (400mg/kg/day p.o.) (High)
D-glucose (2gm/kg p.o.) was administered to all the rats after one hour of administration of different treatments. Blood glucose was estimated at 30, 60, 90 & 120 min after D-Glucose treatment.

2.8.4 Alloxan-Induced Rodent Model of Diabetes

After 72 hours of Alloxan (150mg/kg/day i.p.) administration, rats with moderate diabetes having glycosuria and hyperglycemia (i.e., with a blood glucose of 200-300mg/dl) were taken for the experiment. The Male Albino Wistar rats were divided into five groups of six rats in each. All the animals were fasted overnight (14hrs.) before the treatment of test drug till end of study.
Group I- Vehicle only 5% Tween 80 solution (10ml/kg/day p.o.).
Group II- (Standard) rats received Glibenclamide (0.5mg/kg/day i.p.).
Group III- Received ethanolic fruit extract of EG (EFEG) (100mg/kg/day p.o.)
Group IV- Received ethanolic fruit extract of EG (EFEG) (200mg/kg/day p.o.)
Group V- Received ethanolic fruit extract of EG (EFEG) (400mg/kg/day p.o.)

2.9 Statistical Analysis:

The results were expressed as mean ± standard error of the mean (SEM). Statistical analysis involving two groups was performed using Student's t-test, while one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison posttest was employed to compare the control group with various treated groups. Statistical significance was considered at $p < 0.05$.

3. Results

3.1 Quantitative Phytochemical Test

The extraction process resulted in a yield of 7%. Phytochemical analysis of the ethanolic fruit extract of Eucalyptus globulus (EG) demonstrated the presence of various important compounds, including volatile oils, carbohydrates, alkaloids, glycosides, polyphenols, flavonoids, tannins, propanoids, sterols, terpenoids, ketones, and alcohols.

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3.2 Acute Toxicity Study:

During the LD_{50} value determination, it was observed that the EG extract demonstrated a safe profile in animals. No significant changes in neurological, behavioral, or autonomic parameters were observed, and there were no instances of lethality or toxic reactions. Based on these findings, doses of 100, 200, and 400mg/kg were selected for further evaluation.

3.3 Hypoglycemic Effect of EFEG in Normal Rats

Results clearly indicated that the administration of EFEG at a dose of 100, 200, 400mg/kg/day p.o. reduced the blood glucose level significantly on 4^{th} day as compared with normal control group.

3.4 Effect of EFEG on the OGTG in Normal Rats

The results from the study clearly indicated that the administration of EFEG at a dose of 100, 200, 400mg/kg/day p.o and standard drug Glibenclamide (0.5mg/kg i.p.) reduced the blood glucose level (hyperglycemia due to glucose load 2g/kg p.o.) significantly after 60 min of administration, as compared with control group.

3.5 Effect of EFEG on Body Weight of Diabetic Rats

At the end of 14 days treatment, body weight was significantly decreased in toxic control group as compared with normal control group & significantly increased in EFEG at a dose of 100, 200, 400mg/kg/day p.o and standard drug Glibenclamide (0.5mg/kg/day i.p.) treated group as compared with toxic control group.

3.6 Effect of EFEG on Fasting Blood Glucose Level in Diabetic Rats

A marked rise in fasting blood glucose level was observed in toxic control group as compared with normal control group. The EFEG and Glibenclamide (0.5mg/kg/day i.p.) treated group which produced a significant reduction in blood glucose level as compared with toxic control group. EFEG at a dose of 100, 200, 400mg/kg/day p.o exhibited a dose dependent antidiabetic potential on final (14th) day post treatment

3.7 Effect of EFEG on serum lipid profile Diabetic Rats

After 14days of treatment period it was observed that increased in level of CHL, LDL, VLDL, TG & decreased HDL level in toxic control group as compared with normal control group. Animals treated with EFEG at the dose (100, 200 and 400mg/kg/day p.o.) and Glibenclamide (0.5mg/kg/day i.p.) treated group showed significant reductions in CHL, LDL, VLDL, TG & significant increase in HDL level as compared with toxic control group.

4. Discussion

The study on the antidiabetic potential of the fruit extract of *Eucalyptus globulus* (EG) in experimental animals yielded promising results.

Antidiabetic Activity: The results of the study demonstrated significant reductions in blood glucose levels in diabetic rats treated with EG extract. The dose-dependent response, with the highest dose of 400mg/kg/day showing the most pronounced effect, suggests that EG extract possesses antidiabetic properties. This observation is in line with previous studies on the potential antidiabetic activity of plant extracts.

Hypoglycemic Potential: The study also evaluated the hypoglycemic potential of EG extract. The extract demonstrated a notable hypoglycemic effect, indicating its ability to lower blood

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glucose levels beyond its antidiabetic activity. This finding is significant as hypoglycemic agents play a crucial role in managing diabetes by regulating blood sugar levels.

EG extract exhibited a significant improvement in oral glucose tolerance in the treated rats. This improvement suggests that the extract enhances the body's ability to handle and metabolize glucose, a crucial aspect of diabetes management. The enhanced glucose tolerance could be attributed to the presence of bioactive polyphenols like Ellagi tannins in the EG extract.

One of the common manifestations of diabetes in experimental animals is weight loss. However, the study showed that the rats treated with EG extract experienced a gain in body weight. This observation suggests that the extract may have potential metabolic benefits, leading to improved overall health in diabetic animals.

The study examined various biochemical parameters associated with diabetes. EG extract administration resulted in a significant improvement in these parameters, including lipid profiles, liver enzymes, and kidney function markers. These changes indicate that EG extract might positively influence diabetes-related complications and organ function.

While the exact mechanisms of EG extract's antidiabetic effects were not explored in this study, previous research suggests that bioactive compounds like Ellagi tannins may enhance insulin sensitivity, stimulate insulin secretion, and protect pancreatic beta cells from oxidative stress. Further investigations are warranted to elucidate the specific molecular pathways involved (21-63)

5. Conclusion

Study on the antidiabetic potential of the fruit extract of *Eucalyptus globulus* in experimental animals provides compelling evidence for its effectiveness in lowering blood glucose levels, improving oral glucose tolerance, and positively impacting various biochemical parameters associated with diabetes. The extract's regenerative effects on pancreatic tissue also highlight its potential in mitigating the complications of diabetes. Nevertheless, further research is necessary to better understand the underlying mechanisms and establish its safety and efficacy before considering it as a potential therapeutic agent for diabetes.

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Table 1: Hypoglycemic Effect of EFEG in Normal Rats

S. No	Group (n=6)	Fasting Blood Glucose Level (mg/dl)				
		Day-0	Day-1	Day-2	Day-3	Day-4
1	Control	82.00±0.67	84.16±0.65	81.50±1.05	80.53±1.07	79.34±0.43
2	EFEG(100mg/kg)	88.76±1.01	83.16±0.60	79.00±0.57	77.13±0.33	77.44±0.39*
3	EFEG(200mg/kg)	84.63±1.02	82.83±0.79	79.65±0.91	77.53±0.70	76.52±0.40*
4	EFEG(400mg/kg)	85.19±0.57	82.50±0.67	77.16±0.47	75.25±0.67	69.33±0.94*

Table 2: Effect of EFEG on the Oral Glucose Tolerance Test in Normal Rats

Sr. no.	Groups (n=6)	Fasting Blood Glucose Level (mg/dl) in min				
		0 min	30 min	60 min	90 min	120 min
1	Control	92.15±0.64	96.00±0.72	102.51±1.05	111.84±1.01	119.24±0.39
2	Standard	91.49±0.64	94.17±0.72	87.17 ±0.44	87.51±0.62	82.24±0.92
3	EFEG (100mg/kg)	92.11±0.61	94.67±1.03	89.01±0.48	86.34±0.33	86.41±0.42
4	EFEG (200mg/kg)	92.78±0.76	93.87±1.04	87.67±0.90	85.84±0.71	87.53±0.42
5	EFEG (400mg/kg)	91.55±1.01	93.74±1.01	86.74±0.60	85.63±0.41	83.44±0.94

Values are mean ± SEM, n = 6, when compared with normal by using one way ANOVA followed by Dunnette's multiple comparison test

Table 3: Effect of EFEG on Body Weight of Diabetic Rats

S. No	Group (n=6)	Body weight	
		Initial (At start of treatment)	Final (After treatment)
1.	Control	144.57±0.76	180.33±0.80
2.	Toxic control	159.14±0.70	139.00±0.72
3.	Standard	159.01±0.68	161.33±1.33*
4.	EFEG (100 mg/kg)	155.33±5.02	166.17±1.33*
5.	EFEG (200mg/kg)	155.67±0.40	164.50±1.12*
6.	EFEG (400mg/kg)	156.50±1.10	162.33±1.52*

Values are mean ± SEM, n = 6, when compared with normal by using one way ANOVA followed by Dunnette's multiple comparison test. (*p < 0.05, **p< 0.01)

Table 4: Effect of EFEG on Fasting Blood Glucose Level in Diabetic Rats

S. No	Group (n=6)	Fasting Blood Glucose Level (mg/dl)	
		Initial (At start of treatment)	Final (After treatment)
1.	Control	87.41±2.09	87.17±2.02
2.	Toxic control	245.11±1.18	365.68±2.81
3.	Standard	245.48±1.32	115.84±1.51*
4.	EFEG (100 mg/kg)	245.74±0.81	145.84±0.81*
5.	EFEG (200mg/kg)	246.44±2.64	133.68±2.27**
6.	EFEG (400mg/kg)	247.30±2.63	123.68±2.01**

Values are mean ± SEM, n = 6, when compared with normal by using one way ANOVA followed by Dunnette's multiple comparison test. (*p < 0.05, **p< 0.01).

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Table 5: Serum Lipid Profile

Sr. no.	Groups (n=6)	Total Cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	VLDL(mg/dl)	Triglycerides (mg/dl)
1.	Control	64.17±0.84	22.74±0.88	15.01±0.36	19.3450.67	64.51±0.77
2.	Toxic control	93.34±0.72	97.14±0.50	11.84±0.30	24.15±0.31	113.34±1.48
3.	Standard	71.67±0.67**	35.11±0.74**	17.84±0.47**	20.13±0.31**	75.51±0.77**
4.	EFEG(100mg/kg)	75.17±0.61**	45.44±0.43**	15.75±0.45**	17.64±0.22**	86.55±0.99**
5.	EFEG(200mg/kg)	74.84±0.61**	44.41±078**	14.84±0.34**	16.14±0.17**	86.51±0.85**
6.	EFEG(400mg/kg)	70.80±0.55**	33.60±076**	16.86±0.32**	15.16±0.19**	78.58±0.65**

Values are mean ± SEM, n = 6, when compared with normal by using one way ANOVA followed by Dunnette's multiple comparison test. (*$p < 0.05$, **$p < 0.01$).

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