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Antidiabetic Activity of Coccinia Grandis fruit extract in streptozotocin Induced diabetic rats

[1]N. Jagannath, [2]Dr.D. Sheela, [3]Dr.Rohit Dixit

[1]PhD Scholar, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha deemed university, Thandalam, Chennai.602105, Email Id- jagan.jae@gmail.com

[2]Associate Professor, Dept of Pharmacology, Saveetha Institute of Medical and Technical Sciences, (SIMATS), Saveetha deemed university, Thandalam, Chennai.602105

[3]Professor, Department of Pharmacology, S.V.S medical college, Mahabubnagar, Telangana.

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Abstract

This study investigates the antidiabetic activity of Coccinia grandis fruit extract in a streptozotocin (STZ)-induced diabetic rat model, utilizing five groups to assess its efficacy. Wistar albino rats were divided into five groups: Group I (normal control), Group II (diabetic control), Group III (diabetic + glibenclamide at 5mg/kg b.wt./day orally), Group IV (diabetic + Coccinia grandis fruit extract at 250 mg/kg), and Group V (diabetic + Coccinia grandis fruit extract at 250 mg/kg). The extract was administered orally for 28 days, and various parameters including fasting blood glucose levels, Random blood glucose, serum insulin, HbA1c, C-Peptide levels and histopathological changes in pancreatic tissues were evaluated. The results showed a significant reduction in fasting blood glucose levels in Groups III, IV, and V compared to the diabetic control group. Serum insulin and C-Peptide levels were significantly increased in Groups III, IV, and V, indicating improved pancreatic beta-cell function. Treating diabetic rats with Coccinia grandis fruit led to a significant reduction in HbA1C levels. This could be attributed to an improvement in glucose metabolism and glycemic control. Histopathological analysis revealed regeneration of pancreatic beta-cells and improved islet morphology in treated groups. Overall, Coccinia grandis fruit extract showed promising antidiabetic activity, highlighting its potential as a natural alternative for diabetes management.

Key words: Diabetes, Coccinia grandis, Natrural medicine, Wistar rats

Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is a global health concern with increasing prevalence and significant morbidity and mortality rates. The management of diabetes involves lifestyle modifications, pharmacological interventions, and, in some cases, insulin therapy. However, the search for effective and safe antidiabetic agents, especially from natural sources, continues to be of great interest (1).

Coccinia grandis, commonly known as ivy gourd or kundru, is a tropical vine belonging to the Cucurbitaceae family. It is widely distributed in tropical and subtropical regions of Asia, Africa, and Australia. The plant is cultivated for its edible fruits, which are used in various culinary preparations and traditional medicines (2).Wistar albino rats were used in this study due to their physiological similarities to humans and the ease of handling and maintenance in laboratory settings.

Studies have shown that Coccinia grandis fruits contain bioactive compounds such as alkaloids, flavonoids, glycosides, phenolic compounds, and terpenoids, which contribute to their medicinal properties. These compounds have been investigated for their potential therapeutic effects in various diseases, including diabetes, cardiovascular disorders, and cancer.(3)

Coccinia grandis, commonly known as ivy gourd or kundru, has been used in traditional medicine for its medicinal properties, with various parts of the plant, including the fruits, leaves, and roots, being utilized to treat different ailments. One of its key attributes is its antioxidant properties, which are believed to protect the body from oxidative stress and reduce the risk of chronic diseases. Studies have demonstrated that Coccinia grandis extracts possess strong antioxidant activity, likely due to their phenolic and flavonoid content(4). Additionally, the plant exhibits anti-inflammatory effects, potentially aiding in the reduction of inflammation and associated conditions. Research has indicated that Coccinia grandis extracts can inhibit inflammatory mediators, showcasing its anti-inflammatory potential(5). Moreover, Coccinia grandis is recognized for its antimicrobial properties, making it effective against various infections caused by bacteria, viruses, and fungi. Studies have confirmed its antibacterial, antiviral, and antifungal activities, highlighting its usefulness in combating infections(6,7). Furthermore, Coccinia grandis is believed to have hepatoprotective effects, shielding the liver from damage and enhancing its function(8). Research has shown that extracts of Coccinia grandis can protect the liver from harmful substances and improve its overall function in animal models(9). Although more research is needed, some studies suggest that Coccinia grandis may

have anti-cancer properties. Initial studies have indicated that extracts of Coccinia grandis can inhibit the growth of cancer cells and induce apoptosis, suggesting a potential role in cancer prevention and treatment(10).The aim of the present study is to assess the antidiabetic activity of Coccinia grandis fruits in Wistar albino rats.

Understanding the antidiabetic activity of Coccinia grandis fruits in Wistar albino rats is crucial for validating its traditional use and exploring its therapeutic potential as a natural remedy for diabetes. This study will contribute to the existing body of knowledge on natural antidiabetic agents and may provide insights for the development of new therapeutic strategies for diabetes management.

Materials and Methods Animal Studies

Animals

All animal experiments conducted in this study were carried out following the guidelines outlined by the Organisation for Economic Co-operation and Development (OECD) for animal testing. Approval for the study was obtained from the Institutional Animal Ethical Committee at SVSMC, Mahabubnagar, under the ethical project number SVSMC/IAEC no.2/2020 /648/A. Before the commencement of the experiments, the animals underwent thorough examination and were given time to acclimatize to their new surroundings. This acclimatization period was crucial to minimize stress and establish a stable baseline for the study. Albino rats weighing approximately 150-190 grams were used as animal subjects and were housed under controlled conditions with a temperature of 22 ± 3° C and relative humidity between 30% and 70%. The rats were maintained on a 12-hour light/dark cycle to mimic natural day-night conditions.

Plant Material

In this research, fruits of coccinia grandis were sourced from the Local Market. To ensure accuracy and authenticity, a Botanist, serving as an Assistant Professor in the Department of Botany at S.V. University in Tirupati, conducted the identification and authentication process. The plant sample bearing fruits of Coccinia grandis was assigned voucher number 0579 for future verification.

The extraction process began by drying the freshly collected fruits of coccinia grandis in the shade. Once dried, the leaves were coarsely powdered and sieved through a 40-mesh sieve to obtain a fine powder. This powdered material was then stored in an airtight container for later use.

For the extraction of active compounds, 100g of the dried material powder was macerated in a hydro-alcoholic solution containing 60% ethanol. This maceration process lasted for 7 days to allow the solvent to extract the desired compounds from the plant material.

After the 7-day period, the macerated mixture was filtered to separate the liquid extract from the solid residue. The solvent was then evaporated from the filtered liquid, resulting in the concentrated extract of Coccinia grandis (11).

Diabetes induction

Diabetes was induced in rats by administering a single intraperitoneal injection of streptozotocin (STZ) at a dose of 45 mg/kg body weight, after an overnight fast. The STZ-treated rats were provided with 5% glucose solution for the next 24 hours to prevent hypoglycemia. Blood glucose levels were monitored, and rats with fasting blood glucose levels above 200 mg/dL were considered diabetic (12).

Experimental design:

Group I: Normal control rats receiving isotonic saline without induction of STZ (Normal control).

Group II: Diabetic rats receiving streptozotocin (diabetic control).

Group III: Diabetic rats receiving glibenclamide drug (5mg/kg b.wt./day orally) (Standard group).

Group IV Diabetic rats receiving with Hydro alcoholic extracts of Coccinia grandis fruit extract (HACG) 250 mg/kg once a day.

Group V: Diabetic rats receiving with Hydro alcoholic extracts of Coccinia grandis fruit extract (HACG) 500 mg/kg once a day.

Parameters Assessed

Body weight

The body weight of each rat in every group was measured weekly throughout the experimental period using an electronic weighing balance. This was done to assess the impact of the specific diet on the rats' body weight.

Fasting blood glucose levels

Fasting blood glucose (FBG) levels were assessed on day 1, one week after induction, and on day 29 of the treatment period.

Random blood glucose levels

Random blood glucose levels were monitored on days 1, 7, 14, and 28 of the drug treatment to assess the fluctuations in fasting and random blood glucose levels. Blood drops were collected from the rat tail tip and analyzed using an Accu-Check Glucometer.

Collection of blood samples and pancreas for biochemical and Histopathological analysis of rats

All the animals were treated orally for 28 consecutive days. During the experimental period, During the treatment period, rats also received standard pelleted diet and water ad libitum during treatment. Blood samples were obtained from rats that had fasted overnight using the retro-orbital venepuncture technique. The serum was separated by centrifugation at 3000 rpm for 15 minutes using a LABCENT 5000 centrifuge machine, following a 30-minute period of blood standing at room temperature, in accordance with standard protocols. EDTA vials were used to collect blood samples for the estimation of glycosylated hemoglobin (HbA1C). Plasma insulin and C-peptide levels were determined using enzyme-linked immunosorbent assay kits. Following blood collection, the pancreata were excised, and the tissues were fixed in buffered formalin, sectioned, and prepared for histopathological examination.

Histopathological examination:

Paraffin-embedded pancreas tissue blocks were utilized for a comprehensive histopathological and immunohistochemical evaluation. Sections of the pancreatic tissues were stained with hematoxylin and eosin to examine histopathological changes under a light microscope in all rats.

Results and Discussion

The findings of this study support the potential antidiabetic activity of Coccinia grandis fruit extract in STZ-induced diabetic rats. The results demonstrated significant improvements in various parameters related to diabetes, including fasting blood glucose levels, random blood glucose levels, serum insulin levels, HbA1c and c-peptide levels and histopathological changes in pancreatic tissues. The antidiabetic activity of Coccinia grandis can be compared with that of other plants known for their antidiabetic properties, such as Momordica charantia (bitter melon) (13), Eugenia jambolana (Indian blackberry), Gymnema sylvestre (gurmar), and Trigonella foenum-graecum (fenugreek) (14).

Table 1 displays the bodyweight in both normal and experimental animals at 1, 7, 14, 21 and 29 days following drug treatment. In our study, we found that the body weight on Day 29 was lower compared to the starting point in the Diabetic control group. Both Coccinia grandis fruit

extract and glibenclamide treatment resulted in a substantial decrease in bodyweight compared to diabetic control.

Table 1: The effect of hydroalcholic extract from Coccinia grandis fruit on the body weight of diabetic and non-diabetic rats

DAY	**Normal control**	**Diabetic control**	**Glibinclamide**	**HACG 250mg/kg.bw**	**HACG 500 mg/kg.bw**
1	159 ± 1.79	158 ± 2.90	158 ± 1.01	159 ± 2.15	157 ± 2.64
7	166 ± 0.57	152 ± 2.68	153 ± 1.31	155 ± 2.14	153 ± 1.80
14	170 ± 0.57	143 ± 2.45	150 ± 0.45	152 ± 1.66	150 ± 2.00
21	175 ± 0.93	135 ± 2.37	153 ± 0.72	152 ± 2.08	152 ± 2.16
29	181 ± 0.90	131 ± 2.06	157 ± 0.27	153 ± 2.07	154 ± 2.02

Mean body weight (gms) ± SEM

This study demonstrated that varying concentrations of Coccinia grandis fruit extract (Groups IV, and V) effectively controlled diabetes by significantly regulating random and fasting blood glucose levels in diabetic rats is showed in the table 2 and 3.

Table 2: The effect of hydroalcholic extract from Coccinia grandis fruit on the Fasting blood sugar of diabetic and non-diabetic rats

Days	**Normal control**	**Diabetic control**	**Glibinclamide**	**HACG 250mg/kgbw**	**HACG 500 mg/kgbw**
1	85.9 ± 0.4	255.8 ± 2.64	256.6 ± 2.27	256.5 ± 1.51	254.3 ± 1.85
29	87 ± 0.68	271.8 ± 2.77	98.2 ± 0.69*	122.2 ± 1.15*	104.6 ± 1.15*

Mean body weight (mg/dL) ± SEM; *p<0.05 when compared to negative control. Test drugs at high dose levels were capable to reduce fasting blood sugar significantly

Table 3: The effect of hydroalcholic extract from Coccinia grandis fruit on Random blood glucose levels (mg/dL) of normal and diabetic rats

Day	**Normal control**	**Diabetic control**	**Glibinclamide**	**HACG 250mg/kgbw**	**HACG 500 mg/kgbw**
0	90 ± 1.79	262 ± 2.36	260 ± 0.99	260 ± 3.98	261 ± 1.85
7	91 ± 1.09	285 ± 4.08*	219 ± 1.66*	254 ± 3.13*	231 ± 5.51*

14	90 ± 1.51	305 ± 3.25*	178 ± 2.29*	235 ± 2.00*	206 ± 2.60*
21	91 ± 1.29	320 ± 2.6*	131 ± 3.02*	203 ± 2.50*	159 ± 5.59*
28	91 ± 1.23	331 ± 1.28*	96 ± 1.27*	150 ± 1.82*	110 ± 1.13*

Mean body weight (mg/dL) ± SEM; *p<0.05

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The plasma insulin levels, c-peptide levels and HbA1C levels of both normal and experimental rats were measured. The diabetic rats experienced a notable increase in HbA1C levels, as well as a significant decrease in plasma insulin and c-peptide levels.

STZ, a potent cytotoxic agent, causes diabetes by inflicting damage to pancreatic β-cells, resulting in a decrease in insulin secretion. According to reports, administering medicinal plants to diabetic animals led to an insulinogenic effect.

The administration of Coccinia grandis fruit extract (250 mg/kg.body weight and 500mg/kg body weight) and glibenclamide to diabetic rats reversed the alterations in plasma insulin, c-peptide and HbA1C, bringing them back to a state close to normal ($P < 0.05$). the reukts are showed in table 4.

Table 4: Levels of Serum Insulin, C-Peptide and HbA1C among various treatment groups.

Parameter	**Normal control**	**Diabetic control**	**Glibinclamide**	**HACG 250mg/kgbw**	**HACG 500 mg/kgbw**
Serum Insulin	17.57±0.22	3.68 ± 0.17	14.97 ± 0.14*	9.91±0.2 6*	12.87 ± 028*
C-Peptide	1.68 ± 0.07	0.28 ± 0.05	1.35 ± 0.06*	0.88 ± 0.75*	1.21 ± 0.73*
HbA1C %	3.37 ± 0.09	9.07 ± 0.1	4.27 ± 0.14*	6.22 ± 0.05*	5.22 ± 0.08*

Mean± SEM; *p<0.05: compared to negative control

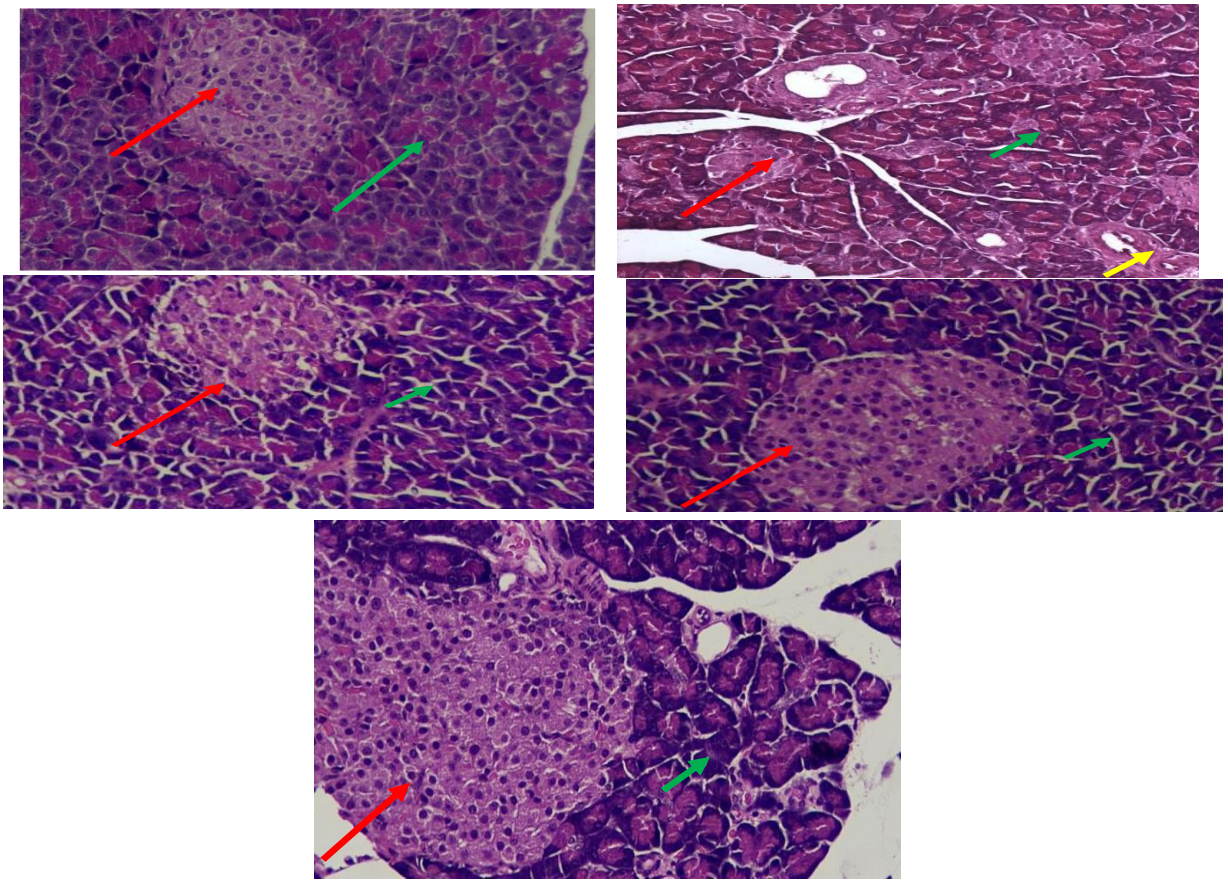
The potential mechanism by which Coccinia grandis fruit extract exerts its antihyperglycemic effect may be Facilitation of insulin secretion from the residual β-cells or regenerated β-cells of the pancreas. The results we obtained align with the findings reported by Pareek et al (15). The presence of elevated levels of C-peptide in diabetic animals treated with Coccinia grandis fruit extract provides additional evidence of the insulin-producing effect of Coccinia grandis fruit extract. C-peptide was measured because it allows for more accurate measurement of the

body's own insulin production, rather than measuring insulin levels in the bloodstream. C-peptide has a significantly longer half-life compared to insulin. Because C-peptide is not easily metabolized, its levels in peripheral venous blood are approximately five to six times higher than insulin levels (16).

Increased non enzymatic glycosylation is one of the possible mechanism linking hyperglycemia and vascular complications of diabetes. During diabetes, the excess glucose present in the blood reacts with hemoglobin to form HbA1C (17). The diabetic rats in the current study exhibited elevated levels of HbA1C in comparison to the normal rats, indicating their inadequate glycemic control. Treating diabetic rats with Coccinia grandis fruit led to a significant reduction in HbA1C levels. This could be attributed to an improvement in glucose metabolism and glycemic control.

Treatment with Coccinia grandis fruit extract in diabetic rats exhibited significant improvement in the pancreatic histoarchitecture leading to a normalization of the tissue structure, regeneration of pancreatic beta-cells and improved islet indicating a potential regenerative effect of Coccinia grandis on pancreatic tissues. This finding is supported by previous research (18).

Figure 1: Histopathological observations of the pancreas of streptozotocin-induced diabetic rats treated with hydro alcoholic extract of Coccinia grandis fruit (HSCG) and glibenclamide



A: Normal control showing normal architecture of acini (AC) - green arrow, beta cells of Islets of Langerhans (IL); **B:** Diabetic control showing necrotic areas, showing shrunken cell mass with vacuolation (Red arrows) in islet of Langerhans (IL) ; (green arrows) acinar cells (AC) and condensed fibers (F) around a blood capillary (yellow arrows); **C:** Diabetic + glibenclamide showing reduction of necrotic areas in beta cells with moderate hyperplastic of islets of acini (AC) -green arrow,beta cells of islets of Langerhans (IL) - red arrow; **D:** Diabetic + HSCG (250 mg/kg.body weight) showing the minimization of the vacuolated cells and a reduction of necrotic areas in beta cells of islet of Langerhans (IL) and with moderate hyperplasia - red arrow and recovery of most normal acinar cells (AC) - green arrow; **E:** Diabetic + HSCG (and 500mg/kg body weight) with showing marked(hyperplasia)mass restoration of β cell of pancreatic islet (IL)- **red arrow** and acinar cells (AC) - **green arrow**-positive sign in improvement

Conclusion

Overall, the findings of this study suggest that Coccinia grandis fruit extract has promising antidiabetic activity against STZ induced diabetic rats possibly through multiple mechanisms including improved insulin secretion, lowered fasting blood glucose levels and glycosylated hemoglobin in blood. Furthermore, the protection of pancreatic beta-cells and proliferation of secretory granules within the cells signifies that the cells underwent stimulation to produce insulin. Further research is warranted to elucidate the exact mechanisms of action and to explore the potential clinical applications of Coccinia grandis in the management of diabetes

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