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Molecular And Biochemical Characterization of The Antidiabetic and Antioxidant Effects of Costus Pictus in Streptozotocin-Induced Experimental Diabetes

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ABSTRACT

In Streptozotocin (STZ)-induced diabetic Wistar rats, the aqueous (CPL-A), hydroalcoholic (CPL-H), and ethanolic (CPL-E) leaf extracts of Costus pictus were evaluated for their antidiabetic, antihyperlipidemic, and antioxidant properties. After receiving a single intraperitoneal dosage of STZ (60 mg/kg) to induce diabetes, the patient received treatment for 30 days. The reference standard was 10 mg/kg of glibenclamide. Blood glucose levels, lipid profiles, oxidative stress markers, and pancreatic histology were evaluated. When compared to the diabetic control, the results showed that all three extracts dramatically reduced blood glucose levels, with CPL-E having the strongest effect. Additionally, lipid irregularities were successfully repaired, particularly by CPL-E and CPL-H, which raised HDL levels while decreasing total cholesterol, triglycerides, LDL, and VLDL. When compared to the diabetic control, the results showed that all three extracts dramatically reduced blood glucose levels, with CPL-E having the strongest effect. Histological findings confirmed the protective effect of CPL extracts on pancreatic tissue. Overall, the ethanolic extract (CPL-E) demonstrated the strongest therapeutic potential, comparable to Glibenclamide. These findings support the traditional use of Costus pictus in diabetes management and highlight its potential as a plant-based alternative for glycaemic control and metabolic regulation. To identify active ingredients and look into underlying mechanisms, more research is advised.

Keywords: *Costus pictus, Diabetes, Inflammation, Oxidative stress, antioxidant*

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1. INTRODUCTION

A chronic metabolic condition, diabetes mellitus is characterized by persistent hyperglycemia caused by abnormalities in either insulin secretion or action, or both. With increasing incidence and prevalence across all age categories, it is one of the most urgent global health concerns. According to the International Diabetes Federation, there are currently over 530 million diabetics worldwide, and over the coming decades, this figure is predicted to increase significantly (IDF, 2023). The two primary forms of the disease are Type 1 diabetes, which results from the autoimmune destruction of pancreatic β-cells, and Type 2 diabetes, which is primarily linked to insulin resistance and relative insulin insufficiency (Group, 2014; Menke et al., 2015).

Chronic hyperglycemia in diabetes causes a host of complications, including retinopathy, neuropathy, nephropathy, and an increased risk of cardiovascular diseases. Dyslipidemia and oxidative stress are two of the primary causes of these problems. Diabetic dyslipidemia causes a decrease in high-density lipoprotein (HDL) and an increase in triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). Furthermore, oxidative stress, which is caused by an excess of reactive oxygen species (ROS) and a weakened antioxidant defense, has a major impact on β-cell malfunction and insulin resistance (Anderson & Zochodne, 2016; Pop-Busui et al., 2016).

Although insulin and oral hypoglycemic medications like sulfonylureas and biguanides are effective pharmacological treatments for diabetes, they are frequently linked to drawbacks such side effects, high cost, and diminished effectiveness over time. This has led to a growing interest in exploring plant-based alternatives that are safer, affordable, and accessible, especially in developing countries. For millennia, medicinal plants have been utilized to treat diabetes in many different cultures. These plants often contain bioactive compounds like flavonoids, alkaloids, tannins, and polyphenols, which exhibit antidiabetic, antioxidant, and lipid-lowering properties (CSIR, 1985; Li et al., 2018; Yang et al., 2011).

A member of the Costaceae family, the "Insulin Plant," or Costus pictus D. Don, has long been utilized in traditional and Ayurvedic medicine to regulate blood sugar levels. Native to India and parts of Southeast Asia, Costus pictus is a perennial plant known for its sweet-tasting, spirally arranged leaves. Preliminary phytochemical screenings have revealed that the leaves are rich in flavonoids, phenolic acids, terpenoids, and glycosides, compounds that have shown potential in modulating carbohydrate metabolism and enhancing antioxidant defense mechanisms (Arfan et al., 2008; CSIR, 1985; Poonia et al., 2007).

Even though Costus pictus has been shown to have hypoglycemic effects in previous research, there are currently few thorough studies evaluating various plant extracts and their effects on histology and biochemistry in experimental diabetes. Thus, this study aims to evaluate the therapeutic efficacy of aqueous, hydroalcoholic, and ethanolic extracts of Costus pictus leaves in Wistar rats with diabetes caused by STZ. The study's main objectives are to evaluate oxidative stress indicators, lipid profiles, blood glucose levels, and histological alterations in pancreatic tissue. The outcome is expected to provide scientific validation to the traditional claims and identify the most effective extract, thereby supporting the development of safe and natural alternatives for diabetes management.

2. EXPERIMENTAL

Plant material and preparation of the extracts:

In August and September, the entire *Costus pictus* (Costaceae) plant was gathered from the Ranchi District in Jharkhand, India. A voucher specimen (09867) was preserved for later use once the plant was identified and confirmed by Dr. S. Mohan Kumar, a botanist in the Department of Botany at Sri Venkateswara University in Tirupati, Andhra Pradesh. A hand grinder was used to powder the leaves after they had been shade-dried. The powdered material was macerated with petroleum ether for 48 hours at room temperature in order to defatten one kilogram of it and ensure complete removal of fatty particles. This procedure was carried out three times. The defatted material was air-dried and subjected to successive Soxhlet extraction using solvents of increasing polarity. With regard to the dried plant material, three extracts were prepared, concentrated under reduced pressure, and yielded 0.75%, 0.81%, and 0.79% w/w, respectively. These extracts were aqueous, hydroalcoholic, and ethanolic. The extracts were labelled CPL-A (aqueous), CPL-H (hydroalcoholic), and CPL-E (ethanolic) and kept at 4 °C.

Animals:

Adult male Wistar rats weighing 150–200 g were used in the study. The animals were obtained from an approved and certified animal house and housed in polypropylene cages at 25 ± 1 °C with a 12-hour light/dark cycle at the institutional animal facility. Prior to the trial, the animals were given a week to get used to the lab setting. They were fed a conventional pellet diet and had unrestricted access to water. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) under protocol number TGH/IAEC/PDF/056/2023. Every procedure followed the guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

Drugs and chemicals:

Sigma Aldrich (St. Louis, MO, USA) provided the streptozotocin (STZ), which is used to cause diabetes in experimental animals, and glibenclamide, a common antidiabetic drug. Both materials were very pure and suitable for studies conducted in vivo. All other chemicals and reagents used in the study, unless specified otherwise, were of analytical grade and supplied by reliable commercial suppliers such SRL Pvt. Ltd. (Mumbai, India) and E. Merck India Ltd. These included solvents, buffers, and other biochemicals necessary for the experimental procedures. All reagents were stored and handled according to manufacturer guidelines to maintain their stability and effectiveness throughout the study.

Acute toxicity study:

The acute oral toxicity of *Costus pictus* leaf extract was evaluated following OECD guideline 425 (OECD, 2008). One adult male Wistar rat every step was chosen at random from a pool of five. The rats were given free access to water and fasted for four hours before being dosed. The extract was taken orally at a 2000 mg/kg limit dose. After being closely watched for the first four hours, the animals were then periodically checked for symptoms of toxicity, including drowsiness, agitation, writhing, convulsions, piloerection, or death, throughout the course of the next twenty-four hours. For a total of 14 days, more observations were made every day.

Diabetes induction:

Ozay et al. (2020) report that in order to develop diabetes in Wistar rats that had fasted overnight, 60 mg/kg of streptozotocin (STZ) prepared in 0.1 M citrate buffer (pH 4.5) was given intraperitoneally once (Ozay et al., 2020). Blood glucose levels were assessed prior to and 48 hours following STZ therapy. Rats having blood glucose levels above 200 mg/dL, which were considered to be diabetic, were included in the study. To reduce mortality, Kohzaki et al. (2008) gave diabetic rats with blood glucose levels more than 450–500 mg/dL one unit of Huminsulin subcutaneously, and two units of those with levels greater than 600 mg/dL (Kohzaki et al., 2008).

Experimental design:

Thirty-six adult Wistar rats were randomly assigned to six groups (n = 6). Group 1 received an oral dosage of 0.1% w/v carboxymethyl cellulose (CMC) as the usual control. Group 2, the diabetic control group, was left untreated after streptozotocin (STZ) induction. Group 3 received Glibenclamide (10 mg/kg, p.o.) once day for 30 days, in compliance with the dosage used in a previous experiment (Reda et al., 2016). Diabetic rats in groups 4, 5, and 6 were given oral doses of 100 mg/kg of Costus pictus leaf (CPL) extracts for 30 days in a row. The extracts were aqueous (CPL-A), hydroalcoholic (CPL-H), and ethanolic (CPL-E), respectively (Reda et al., 2016). The day following the final treatment, body weight and blood glucose levels were measured using an ACCU-Chek glucometer. Following the rats' deaths, the pancreas was taken out, rinsed with ice water, and stored for histological analysis in 10% neutral-buffered formalin.

Group Summary:

The experimental animals were divided into six groups for the study. Group 1 served as the normal control and received 0.1% carboxymethyl cellulose (CMC) as the vehicle. Group 2 was designated as the diabetic control group and was administered streptozotocin (STZ) only to induce diabetes without any treatment. Group 3 received Glibenclamide at a dose of 10 mg/kg and served as the standard treatment group. Group 4 was treated with 100 mg/kg of CPL-A, while Group 5 received 100 mg/kg of CPL-H. Lastly, Group 6 was administered 100 mg/kg of CPL-E. This grouping allowed for a comparative assessment of the therapeutic effects of the test extracts against both normal and diabetic controls, as well as the standard drug.

General Parameters: Blood, Body Weight, and Urine Analysis:

Rats were starved overnight for the duration of the trial, and blood was drawn on day 0 (baseline), 48 hours after the STZ injection, and on days 8, 16, 24, and 30. According to King's (2012) approach, blood glucose levels were measured by pricking the tail vein using a digital glucometer and glucose test strips. For serum biochemical analysis, 0.5–1 mL of blood was drawn on day 30 via the retro-orbital plexus (King, 2012). After administering STZ, body weight was measured to create baseline values. From day 1 to day 30, all groups—control, diabetic, and treated animals—were routinely observed. Rats were put in separate metabolic cages and given a day to adapt before their urine was analyzed. According to King (2012), weekly urine samples were taken from each group in order to establish and track baseline and treatment-related changes (King, 2012).

Biochemical estimation:

Each rat had 0.5–1 mL of blood drawn via the retro-orbital method on day 30 for serum biochemical analysis. According to Finley and Tietz (1996), factors like total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured using standard enzymatic colorimetric kits (Finley & Tietz, 1996).

Histopathological examinations:

Pancreatic tissues were processed, fixed in paraffin, and cut into sections that were 5 µm thick after being stored in 10% neutral-buffered formalin (Culling, 2013). Following Culling's (2013) methodology, the sections were stained with

hematoxylin and eosin (H&E) for microscopic examination. According to the standards established by Tasci and Bozdayi (2007), the proportion of impacted cells was used to grade the degree of damage to the islets of Langerhans: (-) no damage, (+) mild (<25%), (++) moderate (25–50%), and (+++) severe (>50%) (I. Tasci & M. Bozdayi, 2007).

Statistical analysis:

All of the data were displayed using the mean ± standard deviation (SD). For statistical comparisons across groups, one-way ANOVA was followed by Tukey's post hoc test. A p-value of less than 0.05 was considered to be statistically significant. The analysis was carried out using GraphPad Prism software (version 8.01, GraphPad Software Inc., San Diego, USA).

3. RESULTS

Effect on blood glucose levels:

At baseline (day 0), the blood glucose levels of each group were similar. Blood glucose levels in the diabetic control group rose significantly ($p < 0.001$) 48 hours after streptozotocin (STZ) administration and stayed high throughout the study. Treatment with Glibenclamide significantly reduced glucose levels over time, stabilizing around 186 mg/dL by day 30. Among the extract-treated groups, CPL-E showed the most pronounced antihyperglycemic effect, significantly lowering glucose levels from day 16 onward ($p < 0.01$ vs. diabetic control), reaching 222.87 ± 6.97 mg/dL on day 30. Both CPL-H and CPL-A demonstrated statistically significant improvements in glucose levels over time when compared to the diabetes control group (*$p < 0.05$). However, CPL-E exhibited superior glycemic control over CPL-A and CPL-H. These findings suggest that *Costus pictus* ethanolic extract (CPL-E) possesses notable antidiabetic activity and may be more effective than its aqueous and hydroalcoholic counterparts.

Table 1. The effect of CPL-A, CPL-H, and CPL-E on blood glucose levels:

Experimental groups	Blood glucose levels (mg/dl)					
	0 day	48 hrs	8th day	16th day	24th day	30th day
Normal control	93.19±2.28	92.07±2.79	94.07±2.99	96.17±2.96	99.37±3.39	104.07±4.47
Diabetic control	91.98±2.21	a318.07±3.27***	a362.17±4.73***	a255.87±7.57***	a265.87±7.77***	a274.87±8.17***
Standard treatment	94.29±2.18	322.67±3.07	254.57±3.88	205.87±5.47	186.20±3.17	186.87±5.37
CPL-A 100 mg/kg	92.37±2.58	212.87±5.47	225.87±3.87	b233.87±6.57*	b239.87±4.77*	b246.87±8.77*
CPL-H 100 mg/kg	94.10±2.38	206.87±10.17	221.87±5.47	b225.87±7.07*	b231.87±7.57*	b235.87±5.57*
CPL-E 100 mg/kg	95.47±2.46	217.87±8.27	216.87±8.37	b223.87±5.17**	b228.87±6.57**	b222.87±6.97**

*Values are expressed as mean ± SD (n = 6). A significant difference from the normal control group is shown by **p < 0.01, *p < 0.001. The letter b indicates a significant difference from the diabetic control group (**p < 0.01, *p < 0.001).*

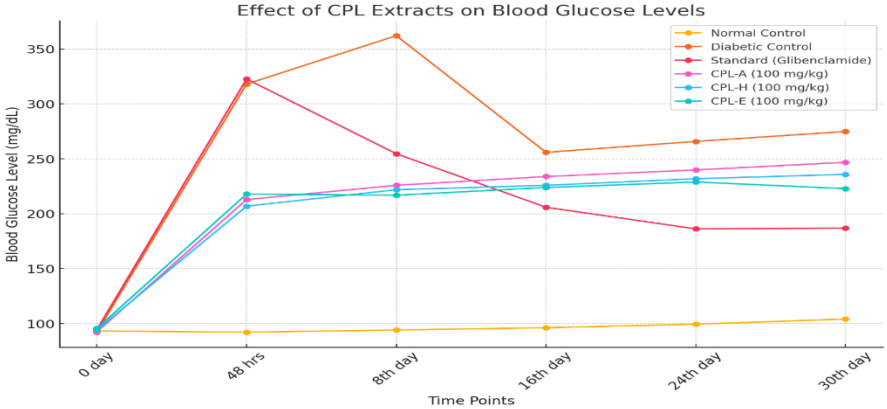

Figure 1. CPL extracts' impact on blood glucose levels

Effect on lipid profile:

Lower HDL levels and higher levels of total cholesterol (TC), triglycerides (TG), LDL, and VLDL than in the normal control group ($p < 0.01$) were indicative of significant dyslipidemia in STZ-induced diabetic rats. Following Glibenclamide treatment, lipid parameters reverted to normal, with levels that were on par with the normal group. CPL-E, CPL-H, and CPL-A extracts at 100 mg/kg significantly improved the lipid profile in comparison to the diabetes control group. All three extracts effectively reduced TC, TG, LDL, and VLDL while increasing HDL levels (*$p < 0.05$, *$p < 0.01$ vs. diabetic control). Compared to CPL-A, CPL-E and CPL-H demonstrated somewhat superior lipid-lowering effects, especially when it came to lowering LDL and VLDL levels. According to these findings, extracts from *Costus pictus*, particularly the ethanolic (CPL-E) and hydroalcoholic (CPL-H) forms, show encouraging antihyperlipidemic action in diabetic patients.

Table 2. CPL-A, CPL-H, and CPL-E's impact on the lipid profile

Groups	TC (U/l)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal control	65.47±2.68	36.07±2.83	17.37±1.27	59.07±2.91	11.10±1.34
Diabetic control	a75.37±2.38**	a44.97±2.81**	a15.97±1.08**	a72.37±2.35**	a13.50±1.33**
Standard treatment	66.07±3.91	37.27±2.92	17.87±1.17	62.47±3.05	11.69±1.22
CPL-A 100 mg/kg	b68.57±1.92*	b38.57±2.23*	b17.67±1.10*	b63.37±2.26*	11.74±1.17
CPL-H 100 mg/kg	b69.17±2.31*	b37.87±1.83*	b17.87±1.43*	b62.67±3.12**	b11.25±1.24*
CPL-E 100 mg/kg	b68.67±2.59*	b37.17±1.28*	b17.67±1.08*	b62.37±2.52**	b11.32±1.03*

*Values are expressed as mean ± SD (n = 6). A significant difference from the normal control group is shown by **$p < 0.01$, *$p < 0.001$. A significant difference from the diabetic control group is shown by b (**$p < 0.01$, *$p < 0.001$). Triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and total cholesterol (TC) are all acronyms.*

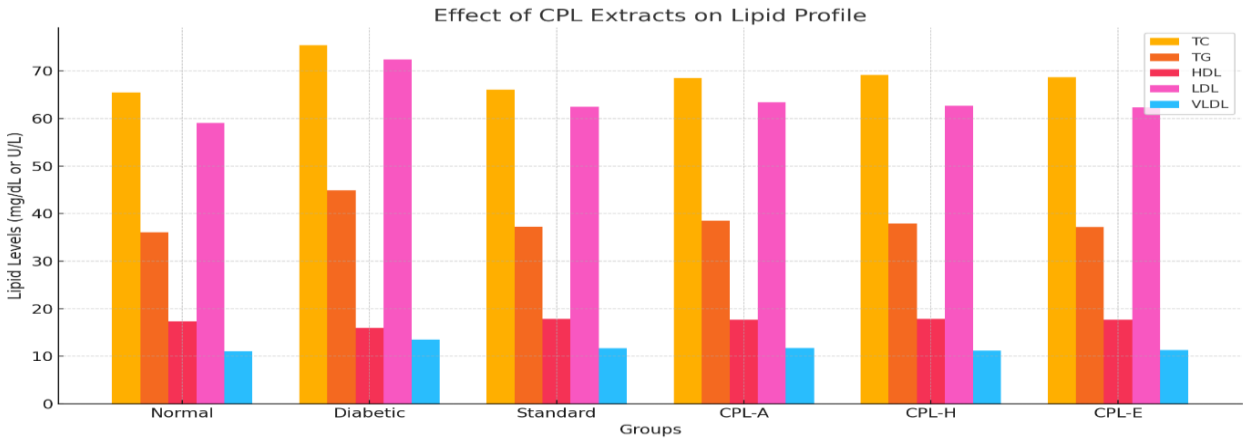

Figure 2. Effect of CPL Extracts on lipid profile

Assessment of oxidative stress markers:

In diabetic rats, oxidative stress was indicated by a significant decrease in catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH) and a significant increase in thiobarbituric acid reactive substances (TBARS) as compared to the normal group (*$p < 0.001$). These findings reflect impaired antioxidant defence and increased lipid peroxidation due to STZ-induced diabetes. Glibenclamide treatment significantly restored antioxidant enzyme levels and reduced TBARS

levels (*p < 0.001). CPL-E had the most notable antioxidant effect of the *Costus pictus* leaf extracts, almost matching the standard medicine by significantly raising CAT, SOD, and GSH while lowering TBARS (**p < 0.01 to *p < 0.001 vs. diabetes group). Strong improvements were also obtained by CPL-H, while CPL-A had minor effects. CPL-E exhibited the strongest antioxidant activity overall, indicating that it may be able to stop the oxidative damage associated with diabetes mellitus.

Table 3. Effect of CPL-A, CPL-H and CPL-E on markers of oxidative stress

	CAT (U/min)	**SOD (U/mg protein)**	**GSH (µM /g tissue)**	**TBARS (nM /min/mg protein)**
Normal Control	7.15±0.92	25.58±1.20	6.82±0.21	32.17±1.31
Diabetes Control	a5.60±0.30***	a14.78±0.88***	a2.59±0.18***	a56.15±1.38***
Standard treatment	b7.68±1.31**	b23.75±0.91***	b6.71±0.64***	b30.93±1.47***
CPL-A 100 mg/kg	b7.32±1.00*	b19.39±1.02**	b5.90±0.56**	b43.90±1.31**
CPL-H 100 mg/kg	b7.52±0.93**	b22.48±1.03***	b6.63±0.60***	b35.15±1.22***
CPL-E 100 mg/kg	b7.61±0.98***	b24.90±0.98***	b6.77±0.47***	b31.14±1.35***

*Values are displayed using Mean ± SD (n = 6). A significant difference from the normal control group is shown by **p < 0.01, *p < 0.001. B indicates a significant difference compared to the diabetic control group (**p < 0.01, *p < 0.001).*

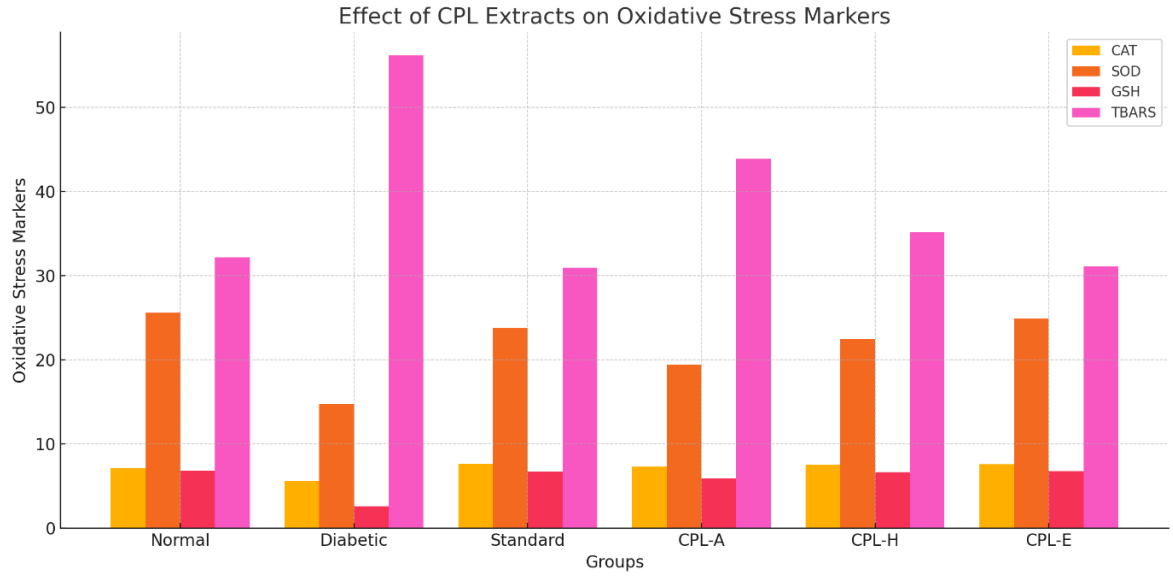

Figure 3. Effect of CPL Extracts on markers of oxidative stress

Histopathological examination:

Histological examination of H&E-stained pancreatic sections revealed clear differences among the experimental groups. The normal control group (A) showed a well-organized cellular architecture and undamaged islets of Langerhans. The diabetes control group (B), on the other hand, displayed significant cellular damage, decreased islet size, and severe degeneration. Treatment with Glibenclamide (C) preserved islet structure with only minor damage, indicating effective protection. Among the extract-treated groups, CPL-E (F) showed the most notable restoration of islet architecture, closely resembling the standard drug group, with minimal cellular disruption. CPL-H (E) also demonstrated considerable improvement, while CPL-A (D) showed moderate protective effects. These findings suggest that *Costus pictus* ethanolic extract (CPL-E) offers significant histological protection to pancreatic tissue in diabetic conditions.

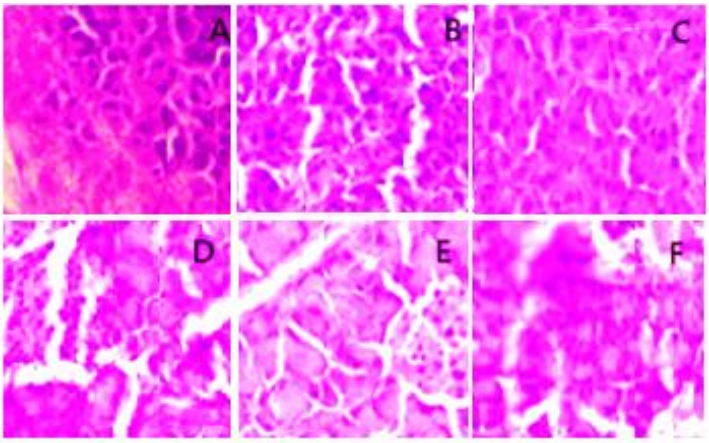

Figure 4. Pancreatic tissue samples from each experimental group that have been H&E-stained (magnification: 200×). Normal control (A), diabetic control (B), and C: 10 mg/kg of glibenclamide; D: 100 mg/kg of CPL-aqueous extract; E: 100 mg/kg of CPL-hydroalcoholic extract; and F: 100 mg/kg of CPL-ethanolic extract.

4. DISCUSSION

The aqueous (CPL-A), hydroalcoholic (CPL-H), and ethanolic (CPL-E) leaf extracts of Costus pictus were evaluated for their antioxidant, antidiabetic, and antihyperlipidemic effects in Wistar rats with STZ-induced diabetes. Due to its specific β-cell cytotoxicity, the STZ model is commonly used to induce type 1 diabetes (Balaha et al., 2018; Deeds et al., 2011), and our results confirmed successful diabetes induction through significantly elevated blood glucose levels. During the 30-day period, blood glucose levels significantly decreased as a result of CPL medication, particularly CPL-E. Among the extracts, CPL-E showed superior glycemic control, suggesting that ethanolic extraction preserved or concentrated key phytoconstituents with hypoglycemic potential. Previous studies have also reported hypoglycemic activity of Costus pictus, attributing it to flavonoids, alkaloids, and triterpenoids present in the leaves (Cherng & Shih, 2006; Wei et al., 2003). Our findings align with these reports, supporting the use of Costus pictus as a natural antidiabetic agent.

The diabetic control group exhibited diabetic dyslipidaemia, which is indicative of metabolic abnormalities common to diabetes mellitus and is defined by increased TG, TC, LDL, and VLDL and decreased HDL. The lipid profile was much enhanced by the extracts, especially CPL-E and CPL-H, which brought it back to normal levels. There have been prior reports of Costus pictus's similar lipid-modulating actions (Liu et al., 2019; Petchi et al., 2013), likely mediated through insulin-sensitizing or lipid metabolism regulatory pathways. The inclusion of phytosterols and polyphenols, which are known to lower cholesterol production and enhance lipid clearance, might be accountable for these effects (Dewanjee et al., 2018; Piconi et al., 2003; Yang et al., 2011). One of the main causes of problems from diabetes is oxidative stress. Rats with diabetes showed increased TBARS and markedly reduced levels of antioxidant enzymes (CAT, SOD, and GSH), suggesting high oxidative stress. Treatment with CPL extracts led to significant restoration of antioxidant status, with CPL-E again showing the most potent effect. These findings are corroborated by past research that indicated Costus pictus's high phenolic component content confers potent antioxidant qualities (Lipinski, 2001; Pitocco et al., 2013). The reduction in TBARS suggests suppression of lipid peroxidation, while the restoration of endogenous antioxidants implies cellular protection.

These biochemical results were then validated by histopathological analysis. The diabetic control group showed significant pancreatic damage, including malformed islets of Langerhans. In contrast, the Glibenclamide and CPL-E treated groups maintained near-normal pancreatic histoarchitecture, indicating β-cell preservation or regeneration. In other experimental diabetic models, plant-based antioxidants have demonstrated similar pancreatic protective properties (Ikewuchi et al., 2009; Pitocco et al., 2013). According to the study's findings, in STZ-induced diabetic rats, Costus pictus leaf extracts - specifically, the ethanolic extract (CPL-E)—show notable antidiabetic, antihyperlipidemic, and antioxidant properties. These effects were similar to those of Glibenclamide, a common antidiabetic medication. The results support the traditional use of Costus pictus and warrant further studies to isolate active constituents and explore molecular mechanisms involved.

5. CONCLUSION

The results of this study show that in STZ-induced diabetic rats, extracts from the leaves of *Costus pictus*, especially the ethanolic extract (CPL-E), have strong antidiabetic, antihyperlipidemic, and antioxidant properties. Of the three extracts that were examined, CPL-E performed similarly to the common medication Glibenclamide in terms of lowering increased blood glucose levels, restoring lipid profiles, and improving oxidative stress measures. Histopathological analysis further confirmed the extract's protective effect on pancreatic tissue, suggesting a potential role in preserving β-cell function. The

inclusion of bioactive substances including flavonoids, phenolics, and triterpenoids—which are known to improve insulin sensitivity, alter lipid metabolism, and fight oxidative stress—may be responsible for the therapeutic effects that have been seen. These findings support *Costus pictus's* potential use as a natural supplementary therapy for diabetes and its consequences and validate its historic use as a medicinal herb that lowers blood sugar. However, to advance its therapeutic use, further investigations are warranted to isolate and characterize the active phytoconstituents, determine long-term safety, and evaluate its efficacy through clinical trials. The study paves the way for developing plant-derived alternatives that can complement existing diabetes treatments while minimizing side effects associated with synthetic drugs.

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