



Research Article

Antidiabetic activity of Hydroalcoholic extract of *Epiphyllum oxypetalum* (Nishagandhi) leaf extract on Alloxan induced Diabetes Mellitus in Rats

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Abstract

Background: Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from impaired insulin secretion, insulin action, or both. It is associated with disturbances in carbohydrate, protein, and lipid metabolism. *Epiphyllum oxypetalum*, commonly known as “Bakawali” or “Bunga Raja,” belongs to the family Cactaceae and is traditionally used in Malay medicine. Objective: The present study aimed to evaluate the antidiabetic activity of *Epiphyllum oxypetalum* leaf extract in alloxan-induced diabetic rats. Methods: Adult male Wistar rats weighing 180–200 g were used for the experimental study. Diabetes mellitus was induced by administration of alloxan. Diabetic animals were treated with *Epiphyllum oxypetalum* leaf extract, and changes in blood glucose levels were assessed. The effects of the extract were compared with those observed in normal and diabetic control groups. Results: Administration of alloxan produced a significant elevation in blood glucose levels, confirming successful induction of experimental diabetes. Treatment with *Epiphyllum oxypetalum* leaf extract produced a beneficial reduction in elevated blood glucose levels in diabetic rats, indicating potential antidiabetic activity. Conclusion: The findings suggest that *Epiphyllum oxypetalum* leaf extract possesses promising antidiabetic properties and may be a potential source of bioactive compounds for managing hyperglycaemia. Further investigations are required to identify the active phytoconstituents and clarify their mechanisms of action.

Keywords: *Epiphyllum oxypetalum*, Diabetes mellitus, Alloxan, Hyperglycaemia, Wistar rats, Antidiabetic activity

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Introduction

Diabetes is a long-term metabolic disease of the lipid, protein, and carbohydrate metabolism that is characterised by elevated blood sugar levels after meals and during fasting (1). Diabetes mellitus is a complicated metabolic disease brought on by either inadequate or insulin dysfunction. Diabetes is a disorder in which an individual has elevated blood sugar (glucose) levels due to insufficient insulin production by the body or improper response of body cells to the insulin that is produced. Diabetes has low likelihood of eradication and requires appropriate treatment, diagnosis, and nutrition. It is described as collection of disorders following elevated risk of vascular disease complications, hyperglycemia, and abnormal metabolism of carbohydrates, lipids

and proteins (3,4,5). Insulin deficiency resulting from lack in beta cells is the etiology of type I diabetes. Patients with Type II diabetes are unable to respond to insulin and can be managed with dietary modifications, medication and exercise. There is significant similarity between type 2 diabetes and gestational diabetes mellitus (GDM), including low insulin response and production. It affects between 2–5% of pregnancies and either gets better or goes away after birth. Ninety percent of people with diabetes have type II diabetes, which is the more prevalent. If type 2 diabetes is not properly treated, it can lead to severe problems such as vascular disease, coronary artery disease, blindness, erectile dysfunction, renal failure, and slow-healing wounds. High blood sugar levels, frequent urination, unusual thirst, excessive weakness and fatigue, weight loss, intense hunger, nausea, impaired vision, vomiting, mood swings, irritability, and other symptoms are possible for both kind of diabetes. Medicinal plants are an important source of medications and constantly represent a vital element of the strategies for many health conditions including Diabetes mellitus. Analysis in 2017 estimates that 425 million people (20–79 years of age) suffered from DM, and it is

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expected by 2045 it may rise to 629 million(6). In developing nations, traditional medicines, which are primarily composed of medicinal herbs, have historically been significant substitutes for modern pharmaceuticals. *Epiphyllum oxypetalum* is available in Bangalore, Uttarakhand, Ranchi, Mumbai and Chennai in India (7). One of the most well-known species in the genus *Epiphyllum* is a fast-growing plant in Cactaceae. Referred as Bramhakamalam in India, known as a holy herb. It is recommended for heart pain and is called as "Pain in the Heart" by the Shoshone tribe in India. It is also referred as the Lady of Night, Nishagandhi, Dutchman's pipe cactus, Queen of the Night etc (8). *Epiphyllum oxypetalum* used for traditional purposes and key compound of traditional medicine of Malay. This herb is frequently involved in treating menometrorrhagia, haemoptysis, and dyspnoea in elderly people. *Epiphyllum oxypetalum* additionally have pain suppressing properties and potency of preventing blood coagulation (9). The phytoconstituents phenolic compounds, saponins, tannins, steroids, terpenoids, glycosides and resins are present in the leaf extract of *Epiphyllum oxypetalum*, but flavonoids, alkaloids, acidic compounds, phlobatanins, and sterols are not(10). The current study performed to analyze the action of *Epiphyllum oxypetalum* on alloxan induced diabetic rats.

Materials and methods

Animals

Male Wistar rats of weight ranging between 180-200g were used for the experiment, ethical clearance was obtained from institutional animal ethical committee and procured from a animal breeder, Biogen Laboratory Animal Facility, registered under Committee for Control and Supervision of Experiments on Animals (CCSEA) (2150/PO/Bt/S/2022/CPCSEA). Every animal was kept in a typical laboratory setting in cages made of polypropylene. Rats received with a regular pellet as food (supplied by the Biogen experimental animal facility) and water *ad-libitum* throughout the process. Institutional Animal Ethical Committee(IAEC) of the CCSEA gave its approval for utilization of animals

Chemicals and Equipment

Alloxan was procured as gift sample from BLD Pharmatech (India) Pvt Ltd. Glibenclamide was procured from aristo pharmaceuticals Pvt Ltd was used as standard drug.

Level of blood glucose was determined by ONE TOUCH equipment which is depended on glucose oxidase principle and values were provided in units of mg/dL.

Collection and authentication of plant materials

The *Epiphyllum oxypetalum*, leaves were obtained from a botanist, identified by Dr. V. Rama Rao, Research officer (Botany) at the Central Ayurveda Research Institute, Bangalore, and were given voucher number SMPU/CARI/BNG/2023-24/2750(4).

Extraction of plant material

The leaves were dried in shade at room temperature. With the aid of blender the dried leaves were reduced in size to a coarse powder. The powder was treated with petroleum ether for removal of fats and impure compounds. The refined powder was then dried and extracted using hydro alcohol (70% ethanol and 30% water)

as a solvent using a Soxhlet extractor at the temperature of 60-80° C. Then the extract obtained was concentrated by a rotary evaporator.(11)

Induction of Diabetes

Alloxan monohydrate suspended in citrate buffer was intraperitoneally given to the rats at dose of 120 mg/kg body weight. To avoid hypoglycemia, they were kept in cages containing 5% glucose solution for the following twenty-four hours. After three days interval rats that had blood glucose levels higher than 150mg/dl were classified as diabetic and used in current study(12,13).

Experimental design

Rats were put into five groups consisting six rats in every group (n=6). Group-I is normal control and treatment with the vehicle. The remaining groups were treated with alloxan by intraperitoneal injection with a dose of 120mg/kg to induce Diabetes mellitus. Group-II kept as Diabetic control. Group-III was treated with Glibenclamide(standard) (5 mg/kg) by oral route(14). Group-IV Animals were receiving the *Epiphyllum oxypetalum* leaves extract at a low dose orally 200mg/kg. and Group-V Animals were receiving the *Epiphyllum oxypetalum* leaves extract at a high dose orally 400mg/kg.

Blood estimations

From tip of rat tail blood was collected to estimate blood glucose level on zero, seventh and fourteenth day. Blood glucose levels were analysed using ONE TOUCH equipment which works on glucoseoxidase principle and outcome was provided in milligrams per deciliter(15,16). On fourteenth day blood was collected via retro-orbital sinus under isoflurane anesthesia. Plasma and serum from blood were separated by centrifuging for 10 minutes at 5000rpm and kept in refrigerator until analysis completed.

Statistical analysis

The program GraphPad Prism 6.0 was used to carry out the statistical analysis. One-way analysis of variance (ANOVA) is performed to compare the values of the normal control and the diabetic control group. Dunnett's comparison test is then used to compare the drug-treated groups with the diabetic control group. p less than 0.05 was deemed significant.

Results

The percentage yield of the extract was found to be 9.76% and was able to dissolve in 1% Tween 80.

Body weight

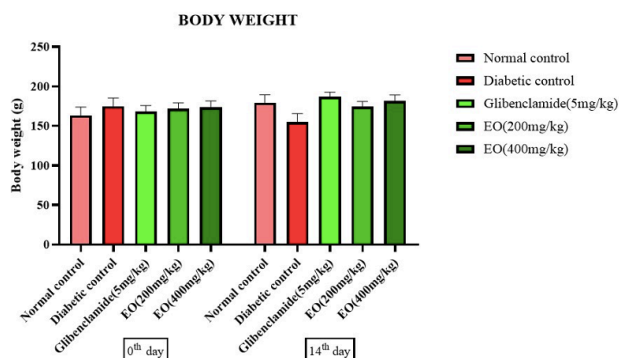
Alloxan is a diabetogenic agent and causes loss of body weight. Treatment with glibenclamide and EO plant extract decreased the elevation in percent of weight loss of diabetic rats. Table 1 illustrates the variations in body weight of normal control, diabetic control and diabetic treatment groups after 14 days. Alloxan significantly reduced the body weight when compared with the controls (p<0.001). Glibenclamide showed slight increase in body weight at significance level (p<0.001) when compared with inducer. Although the extract at 200 mg/kg body weight ameliorated this weight loss at significant level (p<0.01), the extract at 400 mg/kg demonstrated a significant beneficial effect (p<0.001) when compared with inducer.

Table 1: Effect of EO on body weight of alloxan induced diabetic rats

Sl.No.	Groups	Body weight		
		0 th day (g)	14 th day (g)	% increase in body weight
1	Normal control	163.33±4.21	179.16±4.16	9.73±0.59
2	Diabetic control	175±4.28	155±4.28	-11.46±0.28 [#]
3	Glibenclamide(5mg/kg)	168.33±3.07	186.66±2.47	10.94±0.76 ^a
4	EO(200mg/kg)	171.66±3.07	174.16±2.71	1.50±1.01 ^b
5	EO(400mg/kg)	173.33±3.33	181.66±3.07	4.85±0.97 ^a

Values are expressed in mean ± SEM n=6. (p<0.001)[#] vs normal control. (p<0.001)^a, (p<0.01)^b and (p<0.05)^c vs Alloxan inducer.

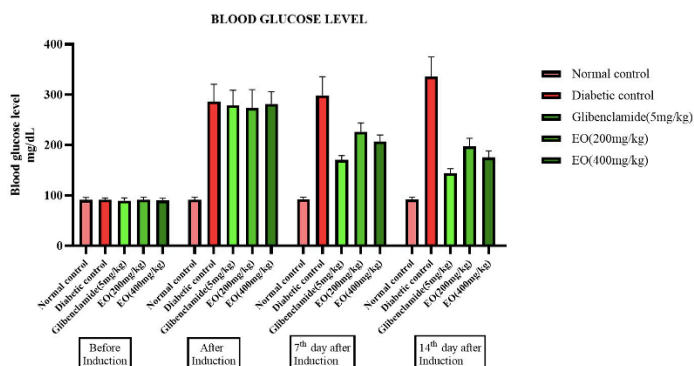
The graphical presentation of the effect of Epiphyllum oxypetalum extract on alloxan induced rats is shown in (Figure 1)

Figure 1: Effect of EO on body weight of alloxan induced diabetic rats**Table 2: Effect of EO on Blood glucose levels of alloxan induced diabetic rats**

Sl.No	Groups	Blood Sugar Level (mg/dl)			
		Before Induction	After Induction	Day 7	Day 14
1	Normal control	90.83±2.10	91.5±2.04	92.66±1.58	91.83±1.85
2	Diabetic control	91.33±1.45	286.5±13.94 [#]	298.66±15.12 [#]	335.66±15.92 [#]
3	Glibenclamide(5mg/kg)	89.66±2.20	278.66±12.31 [#]	170.16±3.56 ^a	143.66±3.89 ^a
4	EO(200mg/kg)	91.66±1.97	273.83±14.77 [#]	226.5±7.09 ^a	197.83±6.37 ^a
5	EO(400mg/kg)	90.16±1.66	281.5±9.84 [#]	207.5±5.16 ^a	175.33±5.28 ^a

Values are expressed in mean ± SEM n=6. (p<0.001)[#] vs normal control. (p<0.001)^a vs Alloxan inducer.

The graphical presentation of the effect of EO on Blood glucose levels of diabetic rats is shown in (Figure 2)

Figure 2: Effect of EO on Blood glucose levels of alloxan induced diabetic rats

Blood glucose levels

Alloxan is diabetogenic compound, cause destruction of beta cells and shows changes in blood glucose levels. The alloxan inducer group caused significant increase in blood glucose level after 72 hours of *i.p* injection. After induction the rats are treated with Glibenclamide and EO plant extract and believed to cause decrease in the levels of blood glucose.

The results indicated that the random blood glucose levels during the experimental period (day 0-14) were significantly higher in alloxan inducer group (p<0.001) when compared with the normal control group. Significantly decreased blood glucose levels were observed in glibenclamide group(5mg/kg) from day 0 to 14 (143.66±3.89) when compared to alloxan inducer group (335.66±15.92). Similarly, blood glucose levels were significantly reduced in hydroalcoholic extract of leaves low dose and high dose (p<0.001) when compared to alloxan inducer group.

Lipid profile

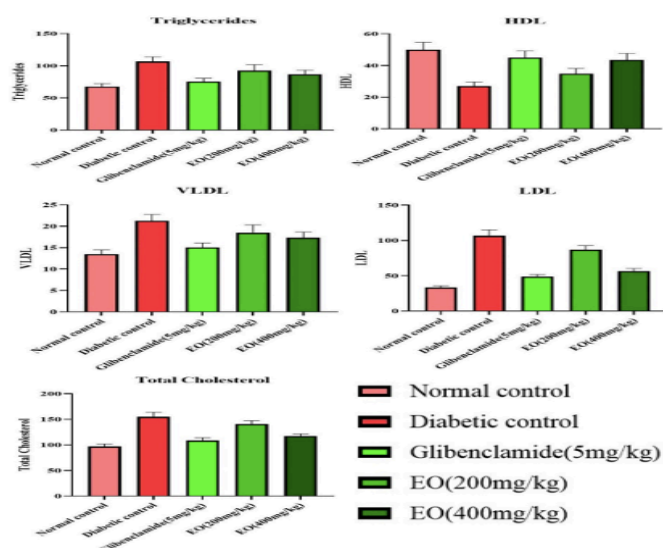
Alloxan induced diabetes cause dyslipidemia resulting in increase of cholesterol, triglyceride and LDL and decreasing HDL. Table 3 shows the serum lipid profile obtained after the 14th dose treatment with hydroalcoholic extract of the leaves. The results show that diabetes, induced by alloxan administration, significantly (p<0.001) raised serum level of cholesterol, triglyceride and LDL. The serum HDL appeared lower (p<0.001) than values of the normal rats. The results also revealed reduced serum level of cholesterol, triglyceride and LDL in the extract treated groups and these reductions were dose-dependent. The highest reduction seen in the highest dose administration (400 mg/kg) group even though these values were, however, significantly higher (p<0.001) than those seen in the normal and Glibenclamide control values. The serum levels of HDL, on the other hand, appeared significantly (p<0.001) raised by the extract administration and again, this elevation was observed to be dose dependent.

Table 3: Effect of EO on lipid profile of alloxan induced diabetic rats

Sl.No.	Treatment	TG (mg/dL)	HDL (mg/dL)	VLDL (mg/dL)	LDL (mg/dL)	TC (mg/dL)
1	Normal control	67.56±1.97	49.93±9.23	13.51±0.39	33.38±1.02	96.83±1.99
2	Diabetic control	106.5±3.02 [#]	26.98±4.63 [#]	21.3±0.60 [#]	106.58±3.42 [#]	154.86±3.67 [#]
3	Glibenclamide (5mg/kg)	75.36±2.08 ^a	44.88±8.24 ^b	15.07±0.41 ^a	48.66±1.47 ^b	108.57±2.27 ^b
4	EO(200mg/kg)	92.48±3.72 ^c	34.75±6 ^c	18.49±0.74 ^c	86.85±2.63 ^c	140.96±2.55 ^c
5	EO(400mg/kg)	86.65±2.68 ^b	43.5±7.87 ^b	17.33±0.53 ^b	56.55±1.70 ^b	117.38±1.69 ^b

Values are expressed in mean ± SEM n=6. (p<0.001)[#] vs normal control. (p<0.001)^a, (p<0.01)^b, (p<0.05)^c vs Alloxan inducer.

The graphical presentation of the effect of EO leaf extract on lipid profile of diabetic rats is shown in (Figure 3)

Figure 3: Effect of EO on Lipid profile of alloxan induced diabetic rats

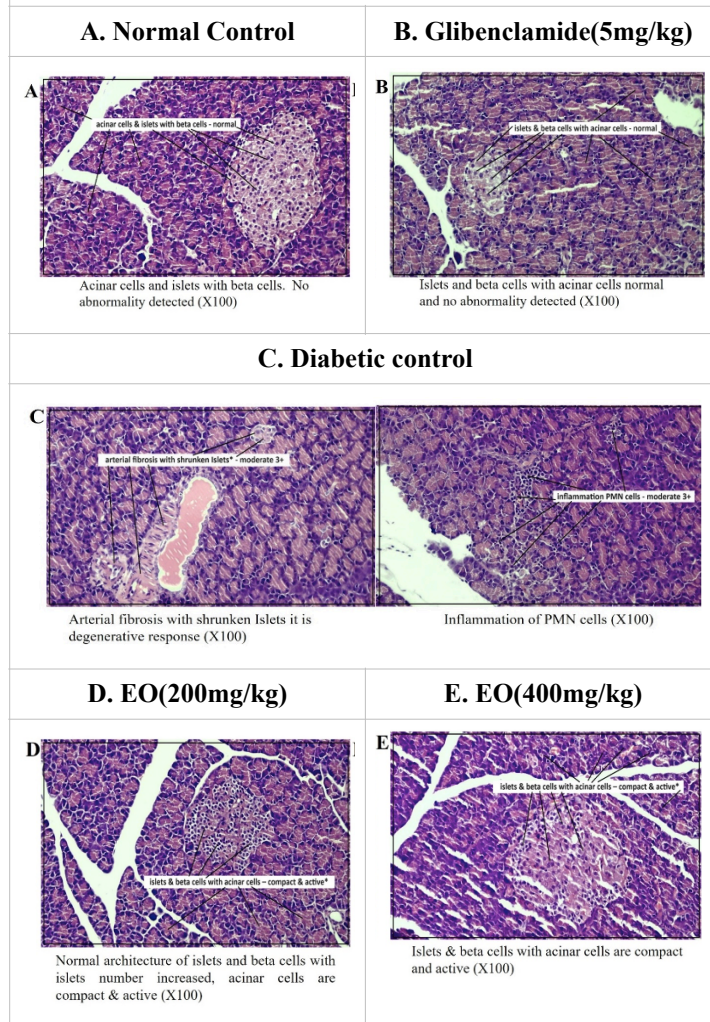
The above figures represent the effect of EO on Lipid Profile of alloxan induced diabetic rats.

Histopathology of Pancreas

The explanation of the below images is shown in the (Table 4)

Table 4: Histopathological observation on Pancreas

Group	Histopathological findings Rat Pancreas
Normal Control	Normal Architecture of acinar cells and islets of Langerhans with beta cells and no abnormality detected.
Diabetic control	Arterial fibrosis and Congestion with inflammation and vacuolar changes with shrunken and ductular hyperplasia of Islets, it is a degenerative vacuolations and inflammation of PMN cells.
Glibenclamide(5mg/kg)	Pancreas showing islets and beta cells with acinar cells.
EO(200mg/kg)	Islets number increased, islets of Langerhans and beta cells with acinar cells are normal, compact and active.
EO(400mg/kg)	Islets and beta cells with acinar cells normal. islets and beta cells with acinar cells are compact and active.

Figure 4: Histopathology of Pancreas

Discussion

Diabetes is now the third largest cause of death rates globally due to a number of pathologic alterations. Diabetes is a metabolic disease that predisposes people to hyperglycaemia by impairing their metabolism of fats, proteins, and carbs. (17) The primary goal of treatment for diabetes is to maintain glucose control in order to avoid micro, macro, and neurological problems. (18) The presence of phytochemicals like phenols, steroids, saponins, glycosides, tannins, terpenoids and resins in hydroalcoholic extract of EO makes the medicinal plants widely utilized for both prevention and the treatment of human ailments. Numerous studies have demonstrated that medicinal plants with hypoglycemic properties work through a variety of processes, such as increasing insulin production, improving target cell insulin sensitivity, and promoting the regeneration of the β -cells in the

pancreatic islets of Langerhans. (19) According to several writers, the antidiabetic action is caused by the presence of phenols, terpenoids, and steroids. (20)

According to studies, certain plant sources include steroids, especially phytosterols, which have been shown to have antidiabetic benefits. By modulating hepatic glucose production and encouraging the liver's synthesis of glycogen, they improve insulin sensitivity and regulate glucose metabolism, which lowers blood sugar levels. (21) Numerous plants contain terpenoids, a broad class of chemical molecules with biologically significant properties. Enzymes essential for the digestion of carbohydrates, like α -amylase and α -glucosidase, can be inhibited by terpenoids. Terpenoids decrease the intestinal absorption of glucose by inhibiting these enzymes. (22) Like terpenoids, phenols can lower postprandial blood glucose levels by inhibiting α -amylase and α -glucosidase. Because chronic inflammation is a major cause of insulin resistance and type 2 diabetes, phenolic substances with anti-inflammatory qualities can help lower it. Certain phenolic substances improve insulin signalling pathways and increase peripheral tissues' absorption of glucose. (23)

Through ROS, alloxan causes diabetes by rapidly destroying beta cells in the pancreas, which results in hyperglycaemia. In turn, hyperglycaemia causes glucose auto-oxidation, which increases the production of free radicals. (24) Glibenclamide, a strong sulfonylurea that is taken orally in tiny amounts to treat type 2 diabetes, stimulates the beta cells in the pancreas, which results in the release of insulin and hypoglycaemia. Human hypoglycaemia has been demonstrated for glibenclamide metabolites 4-trans-hydroxyglibenclamide (M1) and 3-cis-hydroxyglibenclamide (M2). (25) In the alloxan-induced diabetic rats used in this investigation, these combined actions might have equally aided in the release of insulin and regeneration of beta cells. (26)

This study's primary goal was to identify the phytochemicals found in Hydroalcoholic extract of EO leaves. Phenols, steroids, glycosides, saponins, terpenoids, tannins and resins were detected by phytochemical screening. Numerous studies have suggested that phytochemicals are what cause the anti-hyperglycemic action. Determining EO's antihyperglycemic effect in rats with diabetes induced by alloxan was the study's second goal.

The damage to the pancreas in diabetic control rats treated with alloxan (Figure 4(C)) and the regeneration of β cells by glibenclamide (Figure 4(B)) were noted in our investigations. After 14 days of treatment, it is discovered that hydroalcoholic leaf extract of EO at a high dose (400 mg/kg) is more effective than that at a low dose (200 mg/kg). Thus, the explanation above indicates that a high dose of hydroalcoholic leaf extract of EO (400 mg/kg) is more effective and exhibits a therapeutic effect comparable to that of glibenclamide (5 mg/kg). This might be because hydroalcoholic leaf extract of EO may still be able to operate on some β -cells that are still alive to release insulin.

Histopathological investigations support the idea that hydroalcoholic leaf extract of EO may have an antidiabetic effect by promoting pancreatic repair. The control group has normal architecture of acinar cells and islets of Langerhans with beta cells and no abnormality detected, according to histological observations of the pancreas. Alloxan leads to degenerative response and causes inflammation in PMN cells and it induced vascular fibrosis, congestion with inflammation, and vacuolar alterations with reduced islets in diabetic control group. But we can observe that the number of islets grew in both the extract-assisted and standard-treated groups, and the islets and beta cells with acinar cells are "normal, compact, and active" (this could be

because of a favourable response generated by the treatment). This suggests that the EO leaf extract may preserve the pancreatic beta cells and may increase insulin output.

The third goal was to ascertain how hydroalcoholic leaf extract of EO affected the lipid profile in rats with diabetes induced by alloxan. On day 14 of treatment, it was found that the diabetic control group had lower HDL and higher TC, TG, VLDL, and LDL. Excessive fat mobilization from adipose tissue as a result of inadequate glucose utilization causes diabetes-induced hyperlipidemia. TC, TG, LDL, and VLDL levels were considerably lower ($P < 0.05$) in the EO treatment groups (200 mg/kg and 400 mg/kg), whereas HDL levels were significantly higher ($P < 0.05$). Additionally, on the fourteenth day of therapy, the TC and LDL levels for the EO-treated groups were closer to the normal range, and by the fourteenth day of treatment, the 400 mg/kg of EO-treated group had significantly higher HDL levels nearer to the standard (Glibenclamide 5 mg/kg). The suppression of lipid peroxidation and regulation of lipolytic hormones may have resulted from enhanced glucose utilization, as evidenced by a decrease in glucose levels. Numerous plants have been shown to have anti-hyperlipidemic properties in this way.

This specific investigation has shown that the hydroalcoholic extract of EO possesses antihyperglycemic and antihyperlipidemic properties. Sterols, terpenoids, phenols, and other secondary metabolites may be linked to both antihyperglycemic and antihyperlipidemic effects. This makes hydroalcoholic extract of EO's further research and application crucial because many antihyperglycemic medications only lower blood sugar levels without adequately controlling hyperlipidemia. However, more investigation is necessary to determine the precise mechanism of this specific extract, which supports the findings of future research.

Conclusion

In conclusion, the hydroalcoholic extract of *Epiphyllum oxypetalum* leaves, may exhibit promising antidiabetic action on alloxan induced diabetes in rats. Also, the extract positively influenced parameters such as body weight, blood glucose level and serum lipid level, further exerting its ability to treat diabetes conditions. Histopathological examination on pancreatic tissues of rats administered with standard drug and plant leaf extract demonstrates that they involved in curative effect on pancreatic islets and beta-cell integrity when compared to the diabetic group. These outcomes support the utilization of the plant in management of diabetes and provide a basis for further development of novel antidiabetic properties from natural sources. However, extensive research is required to understand fully about the therapeutic potency of this leaf extract and other clinical applications for diabetes mellitus treatment.

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Conflict of Interest: The authors declare no conflict of interest.

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