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RESEARCH ARTICLE

The Curative Effect of *Bryophyllum pinnatum* on Alloxan-induced Diabetes and Lungs Toxicity in Wister Rat

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Abstract

We investigated for the curative properties of *Bryophyllum pinnatum* extract on alloxan-induced diabetes and lung toxicity in adult male Wister rats. The 20 experimental rats used for the study were allocated randomly to 6 groups: normal control (Group 1), negative control (Group 2), low dosage treatment (Group 3), medium-dose treatment (Group 4), and high dose treatment (Group 5). Group 2 was induced with alloxan (20mg/kg, i.p) on days 1 and 5, while Groups 3, 4, and 5 were given alloxan (20mg/kg,i.p) on days 1 and 5, followed by seven days of treatment with an ethanolic extract of *Bryophyllum pinnatum* leaves at 11mg/kg, 22mg/kg, and 33kg/kg, respectively, from days 8 to 14. At the end of the experiment, lung toxicity was measured histo-pathologically by light microscopy and fasting blood glucose levels assayed using spectrophotometry. The blood glucose level of alloxan-exposed rats significantly increased in comparison to the normal control and their basal values, however, the blood glucose levels of rats given alloxan and treatment with *Bryophyllum pinnatum* extract were both decreased relative to normal control. The values for group 1 were paired (Alloxan and *Bryophyllum pinnatum*), and it demonstrated a significant variation ($p<0.05$). Group 2 rats showed mild atelectasis. The other experimental groups' lung showed alveoli dilation. General tissue appears normal in experimental groups. Hence, it was established that *Bryophyllum pinnatum* had an anti-diabetic effect and lung protection against alloxan-induced diabetes and lungs toxicity.

Keywords: *Bryophyllum pinnatum*, Diabetic Complication, Lung Toxicity, Alloxan-Induced Diabetes, Diabetes Mellitus.

1. Introduction

Alterations in the metabolism of fats, proteins, and carbohydrates are indicators of diabetes. It typically comes due to problems with insulin secretion or decreased insulin sensitivity to blood sugar levels [1]. Diabetes causes chronic hyperglycemia, which is linked to prolonged damage, malfunction, and failure of various organs, particularly the kidney, heart, blood vessels, nerves, and eyes [2]. Diabetes is caused by a number of pathologic mechanisms, from autoimmune destruction of the pancreatic β-cells, which results in insulin insufficiency, to anomalies that cause resistance to the action of insulin [2]. The size of the pancreatic islet (PI) and the number of β-cells are less than normal in diabetes individuals and animal models [3]. One effective pharmaceutical strategy for the management of diabetes may be the preservation or restoration of the PI constitution. The islet cells'

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secretion of insulin is the primary pathway for insulin secretion, and it is controlled by voltage-gated Ca2+ channels and K_{ATP} channels [4]. K_{ATP} channels are open when β-cell metabolism inhibits insulin release, but they are closed when insulin is secreted.

Various methods have been used to induce experimental diabetes mellitus in lab animals. Alloxan (31%) and streptozotocin (69%) are arguably of the most commonly utilized drugs. When given parenterally, intravenously, intraperitoneally, or subcutaneously, both drugs can cause diabetes [5]. The dosage of these substances needed to cause diabetes is determined by the nutritional state, route of administration, and animal specials [6].

Streptozotocin (STZ) inhibits cellular reproduction at a dose far lower than that required to inhibit the substrate connection to the DNA or to inhibit any of the enzymes involved in DNA synthesis [7]. It also inhibits DNA synthesis in both mammalian and bacterial cells, causing a unique reaction with cytosine groups in bacterial cells that leads to DNA degeneration and destruction and ultimately the death of mammalian cells. Although STZ is the most widely used drug for causing diabetes in rats, its use in long-term studies has limitations, particularly spontaneous recovery from blood glucose levels, the development of functional insulin, and an elevated prevalence of kidney and liver tumors. These issues are primarily caused by STZ's carcinogenic action [8, 9].

Alloxan is a well-known substance which induces Type-2 Diabetes in animals [5]. Dialuric acid, a byproduct of alloxan reduction created a redox cycle by forming superoxide radicals, which then dismutated into hydrogen peroxide. Reactive oxygen species (ROS) and a massive increase in cytosolic calcium concentration cause β-cells to be destroyed quickly [10, 11]. This can be used as a pathological biomodel to test a substance with purported antioxidant properties in vivo [11].

Regular intake of foods like vegetables is strongly associated with a lower risk for chronic diseases like diabetes, according to epidemiological studies [12]. A growing number of individuals now think that diet directly affects their health [13]. Foods in recent years are designed to promote physical and mental well-being, avoid nutrition-related diseases, and provide necessary nutrients in addition to satisfying hunger [14]. It is often acknowledged that a food's health-promoting qualities can extend beyond its conventional nutritional importance. Bioactive food ingredients that may help prevent chronic diseases like diabetes have received a lot of attention lately [15]. Numerous epidemiologic studies have shown that eating vegetables high in polyphenols is linked to a lower risk of diseases linked to oxidative stress, and a significant body of research has suggested that elevated oxidative damage plays a role in the formation of chronic diseases like diabetes [16, 17]. Therefore, it is necessary to look for anti-diabetic food ingredients that both protect and improve health.

Bryophyllum pinnatum is an upright, succulent, perennial shrub that grows to a height of approximately 1.5 meters and reproduces both vegetatively from leaf bubbils and from seeds. It is a member of the *Grassulaceae* family [18]. Air plant, never die, miracle leaf, and love plant are some of the common names for *Bryophyllum pinnatum*. In tropical Africa, tropical America, India, China, and Australia, it is utilized in traditional medicine. It is widely recognized for its hemostatic and wound-healing qualities [19]. This herb has been used traditionally to treat a variety of illnesses, including anthelmintic, immunosuppressive, hepatoprotective, antinociceptive, anti-inflammatory, anti-diabetic, nephroprotective, antioxidant, antimicrobial, analgesic, anticonvulsant, neuropharmacological, and antipyretic properties [20]. In Bayelsa State, Nigeria, it is used to help a newborn baby's placenta drop [21]. The plant leaf is gently heated, and the juice is extracted and applied to the baby's placenta every day.

Because of their beneficial bioactivity effects, researchers worldwide are very interested in developing novel medications using natural compounds derived from medicinal plants. [22]. Herbs are being increasingly studied as important natural sources for antioxidant and anti-inflammatory substances. Therefore, this work is designed to provide a more available alternative to alleviate the harmful effects, thereby improving health. To evaluate the curative properties of *Bryophyllum pinnatum* extract on alloxan-induced lung toxicity in adult male Wister rat.

2. Materials and Methods

2.1. Collection and Identification of Plant Materials

The fresh *Bryophyllum pinnatum* leaves used in this study were obtained from the Forestry Research Institute of Nigeria (FRIN), Ibadan, Nigeria. They were identified and verified at the Department of Botany's herbarium unit, University of Ibadan, where voucher samples had been deposited under the voucher number UIH-23760.

2.2 Samples Preparation

Fresh leaves of *Bryophyllum pinnatum* were collected, and separated from the stem. The leaves were removed and air-dried at room temperature. The leaves were blended and soaked with ethanol in a closed system using a plate bowl by maceration method. The mixture was stirred for 2 hours, after which it was filtered/sieved with filter paper. The filtrate was put in a beaker transferred into a water bath and left for 48 hours for the ethanol to evaporate. Weight of extract 400 mg.

2.3 Procurement of the Inducement Drug

The drugs (alloxan) used in the study were obtained from a chemical and pharmaceutical store in Benin, Edo state, Nigeria.

2.4 Experimental Animal

Twenty (20) adult Wistar male rats measuring 100-160 grams were purchased and housed in a well-ventilated iron cage in the science laboratory. The rats were housed in regulated settings with a temperature of 28°C, 50% humidity, and 12-hour cycles of light and dark. They were given free access to clean water and normal livestock pellets (Prime Feed Nigeria Limited) for two weeks before the experiment began.

2.5 Ethical Approval

Ethical approval (SMCCN/CREC/2024/017) was duly obtained and the study followed the guidelines of the ethics committee on animal research of Sancta Maria Catholic College of Nursing Sciences, Uzairue, Edo State to carry out this research.

2.6 Experimental Design

Twenty (n=4) adult male Wistar rats of 100-160g were used for this study. They were randomly divided into 5 different groups of 4 rats each. Groups 2, 3, 4, and 5 were induced with diabetes by the intraperitoneal (i.p) injection of 20mg/kg body weight of alloxan monohydrate solution with a disposable insulin syringe. The 5 groups of 4 rats per group as assigned are shown below and summarised in Table 1;

Group 1 (normal control) - Served as the normal control and were administered normal saline.

Group 2 (Alloxan induced group) – Served as negative control, we induced diabetes mellitus with alloxan 20mg/kg on days 1 and 5, and no treatment was given.

Group 3 (Alloxan + low dose of extract) - After administration of Alloxan on days 1 and 5, a low dose of extract (11ml) was administered orally for 8 days.

Group 4 (Alloxan + medium dose of extract) - After administration of Alloxan on days 1 and 5, a medium dose of extract (22ml) was administered orally for 8 days.

Group 5 (Alloxan + High dose of extract) - After administration of Alloxan on days 1 and 5, a high dose of extract (33ml) was administered orally for 8 days.

The administration of extract daily for 7 days, the animals' blood glucose levels were obtained from all mice before the commencement of the experiment by cutting the tail tip and using an Accucheck glucometer and compatible blood glucose test strips.

Table 1. *Experimental design*

Description	Group 1	Group 2	Group 3	Group 4	Group 5
Day 1	Intraperitoneal (I.P) normal saline 0.2ml	Intraperitoneal (I.P) Alloxan 20mg/kg	Intraperitoneal (I.P) Alloxan 20mg/kg	Intraperitoneal (I.P) Alloxan 20mg/kg	Intraperitoneal (I.P) Alloxan 20mg/kg
Day 5	Intraperitoneal (I.P) normal saline 0.2ml	Intraperitoneal (I.P) Alloxan 20mg/kg	Intraperitoneal (I.P) Alloxan 20mg/kg	Intraperitoneal (I.P) Alloxan 20mg/kg	Intraperitoneal (I.P) Alloxan 20mg/kg
Day 8-14	Oral normal saline 0.3ml	Oral normal saline 0.3ml	Oral *B. Pinnatum* 11mg/kg daily	Oral *B. Pinnatum* 22mg/kg daily	Oral *B. Pinnatum* 33mg/kg daily

2.7 Sacrifice of Experimental Animals

All of the study's animals were weighed and killed using the euthanasia method, which involved filling a clear container with woolen cotton soaked in chloroform, placing the animals inside, and closing the container until they passed out. The animals were then dissected using a surgical blade to cut open their thorax and remove the lungs for histological analysis.

2.7.1 Histological Analysis

The rat's lung were carefully dissected out and processed through the stages of fixation in formalin. After fixation, they were dehydrated in increasing concentrations of alcohol and embedded in molten paraffin wax. Sections were and sections were mounted onto a gelatin coated slides then stained using Haematoxylin & Eosin (H&E) stain. Thereafter, slides were viewed using digital light microscope.

2.8. Statistical Analysis

The data collected were recorded at M ± SEM (standard error of mean) and analyzed using SPSS package version 23, ANOVA were used to compare the differences in the means of the various variables

where significant, a post-hoc analysis using tukey test were carried out.

3. Results

3.1. The Effect of Alloxan on the Blood Glucose of Wistar Rats

Table 2. *Blood glucose levels in basal and alloxan-induced diabetic rats.*

Groups	Number of rat	Basal (mg/dl)	Alloxan (mg/dl)	p- value
1	4	98.25 ± 19.60	102.75 ± 14.45	0.186
2	4	79.75 ± 11.50	280.75 ± 108.26	0.031*
3	4	80.50 ± 11.27	121.75 ± 11.53	0.006*
4	4	90.00 ± 13.78	109.67 ± 27.79	0.152
5	4	94.00 ± 10.23	378.67 ± 238.98	0.161

*Value were expressed as Mean ±SEM. *p <0.05 indicates significant difference.*

When compared to the normal control and their baseline values, the experimental results indicate that the fasting blood glucose level of the animals exposed to alloxan increased significantly.The values for group 2 were paired (Basal and Alloxan), it showed a significant difference ($p<0.05$). Also, there were significant differences seen in values for group 3 ($p<0.05$). The rest of the groups showed no significant difference.

3.2 The Effect of *bryophyllum pinnatum* on the Blood Glucose of Wistar Rats

Table 3. *Blood glucose levels in alloxan-induced diabetic rats treated with Bryophyllum pinnatum leaves ethanol extract.*

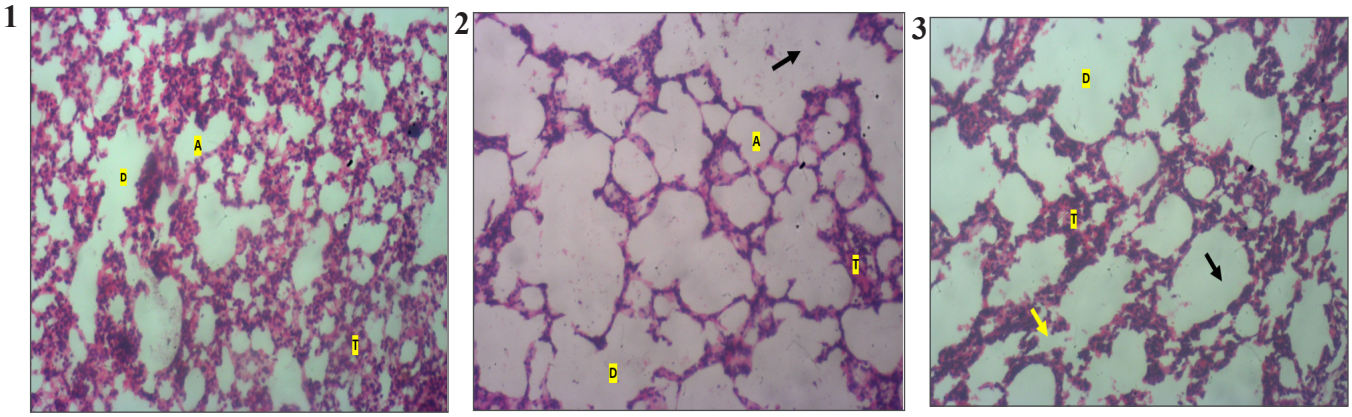
Groups	Number of rat	Alloxan (mg/dL)	*Bryophyllum pinnatum* (mg/dL)	P- value
1	4	102.75 ± 14.45	61.75 ± 4.50	0.018*
2	4	280.75 ± 108.26	167.25 ± 76.33	0.083
3	4	121.75 ± 11.53	215.50 ± 220.22	0.442
4	4	109.67 ± 27.79	88.00 ± 21.00	0.076
5	4	378.67 ± 238.98	98.00 ± 52.05	0.236

*Value were expressed as Mean ±SEM. *p <0.05 indicates significant difference.*

The fasting blood glucose levels of experimental animals were used to estimate the antidiabetic activity of *Bryophyllum pinnatum* leaf ethanol extract (Table 3). While the blood glucose levels of group 1 (normal, non-diabetic) and negative controls group 2 (diabetic) rats remained unchanged during treatment, the blood glucose levels of rats administered alloxan and *Bryophyllum pinnatum* extract both decreased; however, the *Bryophyllum pinnatum*-treated rats' blood glucose levels never recovered to the normal levels seen in group 1.The values for group 1 were paired (Alloxan and *Bryophyllum pinnatum*), it showed a significant difference ($p<0.05$). Also, there were no significant differences seen in treatment values for groups 3 - 5 ($p>0.05$).

3.3 The Effect of Alloxan on the Histoarchitecture of the Lungs

Figure 1 shows Plates 1 to 5, which represents groups 1 to 5 respectively. Rats in group 1 which were given normal saline, photomicrograph revealed normal hepatic histo-architecture as seen in Plate 1 compared with Plate 2. Rats in group 2 induced with alloxan were observed to have mild atelectasis in Plate 2 compared to the rats in the normal control (Plate 1).



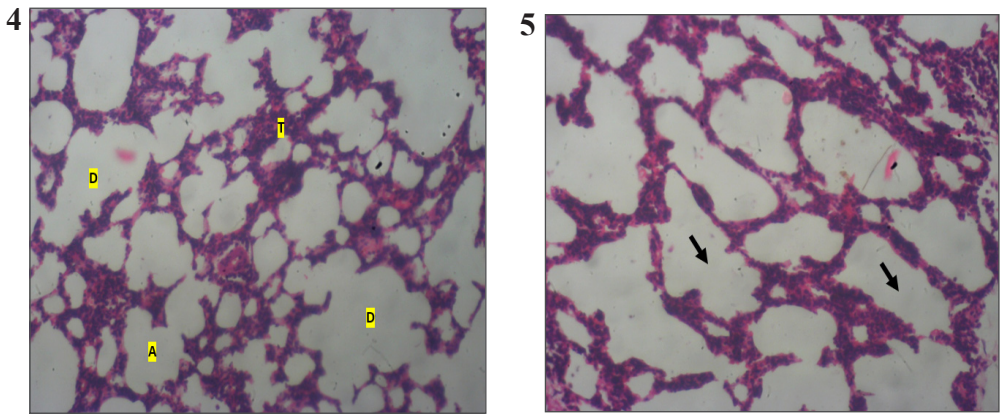


Figure 1. *Plate 1 is a section of the lung from group 1, with normal histo-architecture. It reveals an alveolar duct (D) with several alveoli cells (A) and alveolar connective tissue (T). Plate 2 is a section of the lung from group 2, with mild atelectasis. It also revealed an alveolar duct (D) with several alveoli cells (A) and alveolar connective tissue (T). Plate 3 is a section of the lung from group 3, with alveolar tissue relapse (Yellow arrow) and alveoli dilation (Black arrow). An alveolar duct (D) with several alveoli cells (A) and alveolar connective tissue (T) were seen. Plate 4 is a section of the lung from group 4, with an alveolar duct (D) with several alveoli cells (A) and alveolar connective tissue (T). Other structures appear normal. Plate 5 is a section of the lung from group 5, with dilated alveoli (Arrow). H & E. X300.*

Rats in group 3 treated with low dose of extract (11ml/kg) of *Bryophyllum pinnatum* revealed alveolar tissue relapse and alveoli dilation in Plate 3 compared to the rats in the group 2 (Plate 2) induced with 20mg/kg of alloxan. Rats in group 4 treated with medium dose (22ml/kg) extract of *Bryophyllum pinnatum* revealed normal histoarchitecture of lung tissue in Plate 4 compared to the rats in the group 2 (Plate 2) induced with 20mg/kg of alloxan. Rats in group 5 treated with high dose (33ml/kg) extract of *Bryophyllum pinnatum* revealed dilated alveoli histoarchitecture of lung tissue in Plate 5 compared to the rats in the group 2 (Plate 2) induced with 20mg/kg of alloxan.

4. Discussion

In this present study, we evaluated the curative properties of the extract of *Bryophyllum pinnatum* on alloxan-induced lung toxicity in adult male Wister rats. This decision stems from the fact that alloxan induces type 2 diabetes mellitus, which is prevalent and primarily affects elderly persons [23]. The induction of alloxan increased the blood glucose levels of the rat (Table 2). In our present study, three graded doses of *B. pinnatum* (11 mg/kg, 22 mg/kg, and 33 mg/kg orally) were compared with control (normal saline 0.2 ml orally). The antidiabetic effect of *B. pinnatum* at 22 mg/kg and 33 mg/kg was comparable to normal control, with no significant variation difference between these groups (Table 3). Oral administration of *B. pinnatum* leaf extract reduced the blood glucose levels in rats (mean ± SEM) from 109.67 ± 27.79 (day 7) to 88.00 ± 21.00 (day 14) at the dose of 22 mg/kg while at the dose of 33 mg/kg it reduced from 378.67 ± 238.98 (day 7) to 98.00 ± 52.05 (day 14) in comparison to control (Group 1) as shown in Table 3. The phytochemical(s) in the extract may be the cause of the drop in blood glucose levels. Research has demonstrated that phytoconstituents like flavonoids, glycosides, alkaloids, and carotenoids have strong anti-diabetic effects [24], and quantitative photochemical analyses of *B. pinnatum* leaves showed a significant presence of glycosides, alkaloids, and flavonoids (kaempherol and quercetin) [25]. The results of this study are consistent with those of Nagaratna and Hegde [26], who found that giving rats 200 mg/kg of *B. pinnatum* aqueous leaf extract orally for 28 days significantly ($p < 0.05$) decreased their blood glucose levels. The results of the current investigation demonstrated a non-significant drop in blood glucose levels when compared to controls, despite studies reporting blood glucose-lowering qualities of this plant's crude aqueous extract and supporting its use in treating diabetes [27]. In this work, the ethanol extract of *Bryphyllum pinnatum* leaves was used to bring the elevated blood glucose levels in alloxan-induced diabetic rats down to normal levels.

Alloxan-induced hyperglycemia causes emphysematous changes in conjunction with restriction, and the vascular wall of the muscular pulmonary vessels thickens due to hypertrophy of the tunica media and tunica externa. The light microscopy study shows mild atelectasis, sclerotic alterations in the pulmonary stroma, and damage in the alveolates, which results in the thickening of the interalveolar septa and the collapse of the lung (Plate 2). Experimental animals showed enlargement of lymphoid follicles and lymph nodes in the upper and lower mediastinum. This is because hyperglycemia serves as a basis for the formation of advanced glycation end products, or AGEs, which are byproducts

of impaired glucose metabolism. They attach to the receptors of macrophages, which release cytokines that trigger the immunological response [28, 29].

Since changes in the lungs are primarily caused by microcirculatory disorders in the pulmonary circulation based on the impact of persistent hyperglycemia and are linked to the proinflammatory and proliferative properties of diabetes, we may conclude that microcirculatory disorders indicate the trigger mechanism of lung tissue damages given the described changes in the histoarchitecture [30, 31].

Diabetes spurred by alloxan has a negative impact on the lungs' histoarchitecture both directly and indirectly (via cardiovascular system problems). We must consider the results obtained because the effects of hyperglycemia on the lungs cause morphological remodeling, which in turn leads to the development of respiratory failure as diabetes progresses, whereas the symptoms of adverse effects from prolonged exposure to hyperglycemia can be more noticeable in internal organs like the kidneys, brain, and heart.

This result confirmed the scientific works of Ho *et al*. [32], and Demikhova *et al* [29], which observed alloxan-induced hyperglycemia leads to the development of emphysematous changes in combination with restriction.

The administration of *Bryophyllum pinnatum* revealed alveolar tissue relapse and alveoli dilation (Plates 3 and 5). Samples of lung tissue examined under a light microscope show thickening of the interalveolar septa. The alveolar lumen is free (Plate 4). We discovered collapsing alveoli in addition to emphysematous alterations. In addition to evaluating the toxicity of a single high dose (acute toxicity), it's crucial to evaluate the effects of the medicine over an extended period of time (sub-acute toxicity) and look for information regarding the dangers associated with repeated usage during the phase of drug development.

[33]. A clinical change that could be associated with toxic effects were observed in the high and low dose of *Bryophyllum pinnatum* extract. The lung of animals of both high and low dose groups (Plates 3 and 5) presented alveolar tissue relapse and dilation, indicating the toxic effects. Although the medium dose of the extract preserved a normal cytoarchitecture, indicating the absence of toxic effects. These findings suggest that *Bryophyllum pinnatum* is dose-dependent.

5. Conclusion

The findings gathered show that alloxan-induced hyperglycemia changes the structure of the lung tissue. The lung tissue's parenchymatous component has undergone mosaic changes. They are distinguished by the emergence of emphysematous alterations and the existence of atelectasis sites. Hypertrophic alterations occur in lymphoid tissue and muscle-type arteries. We consequently infer that leaves extract of *Bryophyllum pinnatum* could dramatically lower blood glucose level in a dose-dependent manner.

Conflict of Interest

The authors declare no conflict of interest.

6. References

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