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Histopathological Features of the Pancreas in Alloxan-Induced Diabetic White Rats Treated with Bandotan (*Ageratum conyzoides* L.) Extract

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Abstract

Damage to pancreatic β-cells can lead to hyperglycemia, a hallmark of diabetes mellitus. Ageratum conyzoides L. (bandotan), a plant from the Asteraceae family, is traditionally used in herbal medicine due to its rich content of secondary metabolites. This study aimed to evaluate the histopathological profile of pancreatic tissue in alloxan-induced diabetic rats following treatment with ethanol extract of bandotan leaves. The research employed a true experimental design with a posttest-only control group. A total of 24 white rats were randomly divided into six groups: normal, negative control (aquadest + alloxan), positive control (glibenclamide 0.65 mg/kg BW), and three treatment groups receiving bandotan extract at doses of 100, 200, and 400 mg/kg BW, respectively. Bandotan leaves (4–5 kg) were extracted using ethanol, and histopathological observations were performed under a light microscope at 100x and 400x magnification. Pancreatic damage was scored and analyzed using descriptive statistics. The mean pancreatic damage scores were as follows: negative control group = 1.25; positive control group = 1.00; 100 mg/kg BW group = 1.00; 200 mg/kg BW group = 0.25; 400 mg/kg BW group = 0.00; and normal group = 0.00. The results indicate that the 400 mg/kg BW dose of Ageratum conyzoides L. extract was the most effective in preventing pancreatic damage, with histological features comparable to those of the normal group.

Abstrak

Kerusakan sel β pankreas dapat menyebabkan hiperglikemia, yang merupakan tanda khas diabetes melitus. Tanaman Ageratum conyzoides L. (bandotan) dari famili Asteraceae secara tradisional digunakan sebagai obat herbal karena mengandung berbagai metabolit sekunder. Penelitian ini bertujuan untuk mengevaluasi gambaran histopatologi jaringan pankreas pada tikus diabetes yang diinduksi aloksan setelah pemberian ekstrak etanol daun bandotan. Penelitian ini menggunakan desain eksperimental murni dengan kelompok kontrol posttest only. Sebanyak 24 ekor tikus putih dibagi secara acak ke dalam enam kelompok: kelompok normal, kontrol negatif (aquadest + aloksan), kontrol positif (glibenkamid 0,65 mg/kgBB), serta tiga kelompok perlakuan yang diberi ekstrak bandotan dengan dosis 100, 200, dan 400 mg/kgBB. Daun bandotan sebanyak 4–5 kg diekstraksi menggunakan etanol, dan pengamatan histopatologi dilakukan dengan mikroskop cahaya pada perbesaran 100x dan 400x. Kerusakan pankreas dinilai berdasarkan sistem skor dan dianalisis secara deskriptif. Hasil skor rerata kerusakan pankreas adalah: kelompok kontrol negatif = 1,25; kontrol positif = 1,00; dosis 100 mg/kgBB = 1,00; dosis 200 mg/kgBB = 0,25; dosis 400 mg/kgBB = 0,00; dan kelompok normal = 0,00. Hasil ini menunjukkan bahwa dosis 400 mg/kgBB ekstrak daun Ageratum conyzoides L. merupakan dosis paling efektif dalam mencegah kerusakan pankreas, dengan gambaran histologis serupa dengan kelompok normal.

Keywords: Alloxan, Bandotan leaves, Pancreas, Hystopathological

Kata kunci: Alloxan, Daun Bandotan, Pankreas, Histopatologi

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INTRODUCTION

Diabetes mellitus is a long-term metabolic disease caused by the failure of the pancreas, which plays a crucial role in insulin production, leading to elevated blood glucose levels[1]. When blood sugar levels exceed the normal threshold, this condition is referred to as hyperglycemia. Chronic hyperglycemia can result in progressive damage to various organs, particularly the eyes, kidneys, heart, and nerves[2].

Ageratum conyzoides L., commonly known in Indonesia as daun bandotan, is a plant from the Asteraceae family that is widely used as traditional medicine in Indonesia and many other countries[3,4]. This

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plant grows easily in various types of soil and is characterized by fine, white, hairy leaves and flowers with a white base and blue to purple tips[5].

Phytochemical analysis reveals that bandotan contains bioactive compounds such as flavonoids, alkaloids, and antioxidants, which possess potential antidiabetic properties[6]. Previous studies have reported that bandotan leaf extract can enhance antioxidant activity and may support the regeneration of damaged pancreatic beta cells. However, the majority of these studies focus on biochemical and glycemic parameters, and only a limited number have explored the histopathological impact of this extract on pancreatic tissue integrity in diabetic models [6,7].

Alloxan is a chemical compound frequently used in experimental diabetes research due to its ability to inhibit glucokinase and induce oxidative stress via free radical formation[8]. This process results in DNA damage and destruction of pancreatic beta cells, ultimately leading to insulin deficiency and persistent hyperglycemia. The pathological changes that occur in the pancreas due to alloxan-induced diabetes include degeneration, necrosis, and infiltration of inflammatory cells in the islets of Langerhans[9].

Histopathological evaluation of the pancreas using hematoxylin-eosin (HE) staining is a standard method that allows for detailed observation of structural and cellular alterations related to pancreatic injury in diabetic conditions[10]. Despite the known pharmacological potential of *Ageratum conyzoides* L., there remains a lack of comprehensive histological evidence demonstrating its protective effects on pancreatic beta cells following alloxan-induced damage[11]. This research aims to address this gap by providing a detailed histopathological analysis of the pancreatic tissue in diabetic rats treated with ethanol extract of bandotan leaves.

METHODOLOGY

This study is a pure experiment with a posttest-only control group design, conducted to determine the effect of ethanol extract of bandotan leaves (*Ageratum conyzoides* L.) on the histopathological picture of the pancreas of alloxan-induced diabetic white rats. Ethanol extract treatment of bandotan leaves was administered to evaluate its effect on pancreatic histopathology.

Tools

The tools used in the research include beaker glass, measuring cup, Erlenmeyer flask, pipette, separating funnel, rotary vacuum evaporator, microscope, analytical balance, blender, stopwatch, dropper pipette, filter paper, syringe, water bath, refrigerator, oral sonde, cotton, gloves, glucometer strip, and glucometer.

Materials

The materials used in the study were bandotan leaves (*Ageratum conyzoides* L.), glucose, distilled water, 96% ethanol, n-hexane, concentrated HCl, magnesium powder, chloroform, H_2SO_4, anhydrous acetic acid, $FeCl_3$, alloxan, syringe, vial, NaCl, ethyl acetate, Dragendorff reagent, Mayer reagent, and Bouchardat reagent.

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Preparation of Bandotan Leaf Extract and Phytochemical Screening

The collection of bandotan leaves was carried out by purposive sampling, including both young and mature leaves. The leaves were washed, cut into small pieces, dried, ground, and sieved. Plant identification was performed at the Herbarium Medanense, University of North Sumatra. The ethanol extract of bandotan leaves was then prepared using the maceration method. A total of 500 grams of dried leaf powder was extracted with 96% ethanol for 3–24 hours, filtered, and evaporated using a rotary vacuum evaporator at 60°C until a thick extract was obtained[12]. Phytochemical screening was conducted to detect the presence of alkaloids, flavonoids, saponins, tannins, terpenoids, and steroids using colorimetric reactions with specific reagents[6].

Grouping and Treatment of Alloxan-Induced Diabetic Rats

This study used 25–30 adult rats that were acclimatized for 7 days in a controlled laboratory environment with adequate access to food and water. After acclimatization, the rats were randomly divided into six groups, each consisting of 4–5 rats, ensuring that the variation in body weight within each group did not exceed 20%. The groups were as follows:

1. Normal Group: given distilled water without any treatment.
2. Negative Control Group: given distilled water and induced with alloxan.
3. Positive Control Group: given glibenclamide at a dose of 0.65 mg/kg BW and induced with alloxan.
4. Treatment Group 1: given bandotan extract at a dose of 100 mg/kg BW and induced with alloxan.
5. Treatment Group 2: given bandotan extract at a dose of 200 mg/kg BW and induced with alloxan.
6. Treatment Group 3: given bandotan extract at a dose of 400 mg/kg BW and induced with alloxan.

Dosage Planning for Extract and Alloxan Induction

Bandotan extract was administered orally at doses of 100, 200, and 400 mg/kgBW. The dose of alloxan used for diabetes induction was 120 mg/kgBW, which was converted to the rat equivalent dose using a conversion factor of 0.018. The administration volume was adjusted based on the body weight of each rat.

Diabetes Induction and Glucose Measurement

Rats were fasted for 8 hours prior to alloxan administration. Blood glucose levels were measured on days 0, 3, 7, and 14 using a glucometer by collecting blood from the tail vein.

Histopathological Examination of the Pancreas

Upon completion of the treatment period, the rats were anesthetized, and surgery was performed to remove the pancreas. The pancreas was fixed in 10% neutral buffered formalin and processed for histopathological slide preparation. The sections were examined under a microscope at 100x and 400x magnification to assess histological changes in the islets of

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Langerhans and acinar cells using a scoring system.

Data Analysis

The pancreatic damage scores were analyzed descriptively using the SPSS version 24 software to illustrate the histopathological profile of the pancreas in alloxan-induced diabetic rats treated with bandotan extract. This descriptive analysis was intended to summarize the scoring data and to provide information regarding the effect of bandotan extract on pancreatic tissue structure in diabetic rats.

RESULT AND DISCUSSION

Phytochemical Screening

Phytochemical screening was conducted to identify the presence of major classes of secondary metabolites in the ethanol extract of bandotan leaves (*Ageratum conyzoides* L.). The screening was performed using standard qualitative methods with specific reagents to detect alkaloids, flavonoids, tannins, saponins, quinones, and triterpenoids/steroids. The results of the phytochemical analysis are presented in Table 1.

Table 1. Phytochemical Screening Result

No	Parameter	Result	Sign
1	Alkaloid	Positive	+
2	Tanin	Positive	+
3	Saponin	Positive	+
4	Flavonoid	Positive	+
5	Quinon	Positive	+
6	Triterpenoid/Steroid	Positive	+

Note: (+) = Contains secondary metabolites
(-) = Does not contain secondary metabolites

The results of the phytochemical screening presented in Table 1 confirm that the ethanol extract of bandotan leaves (*Ageratum conyzoides* L.) contains several major classes of secondary metabolites, including alkaloids, tannins, saponins, flavonoids, quinones, and triterpenoids/steroids [5]. The presence of these bioactive compounds provides a scientific basis for the pharmacological potential of bandotan, particularly its antidiabetic activity [6].

Alkaloids are known for their broad range of biological activities, including their ability to stimulate insulin secretion and protect pancreatic β-cells from oxidative damage[13]. Tannins, as polyphenolic compounds, exhibit strong antioxidant properties that can mitigate oxidative stress and inflammation—both of which are implicated in the pathogenesis of diabetes mellitus [14].

Saponins are also known for their hypoglycemic effects, primarily through enhancing glucose transport and stabilizing cell membranes[15]. Flavonoids have been extensively studied for their antioxidant and anti-inflammatory activities and are capable of improving insulin sensitivity and supporting pancreatic β-cell function.

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Quinones further contribute to the extract's complexity, with their potential cellular protective effects, although their specific role in diabetes requires further investigation [16,17].

Additionally, triterpenoids and steroids are recognized for their antidiabetic effects through modulation of glucose metabolism and inhibition of systemic inflammation. Collectively, this phytochemical profile supports the hypothesis that bandotan leaf extract possesses promising therapeutic potential in the management of diabetes mellitus, particularly by protecting β-cell integrity and reducing blood glucose levels[3].

Histopathological Features of Pancreatic Tissue

Histopathological observations of pancreatic tissue were conducted to evaluate morphological changes in the islets of Langerhans among alloxan-induced diabetic rats following treatment with ethanol extract of bandotan leaves (*Ageratum conyzoides* L.). Tissue sections were stained with Hematoxylin and Eosin (HE) and examined under a light microscope at 100x and 400x magnification. The analysis focused on inflammation, necrosis, edema, and the structural integrity of the islets [10,18].

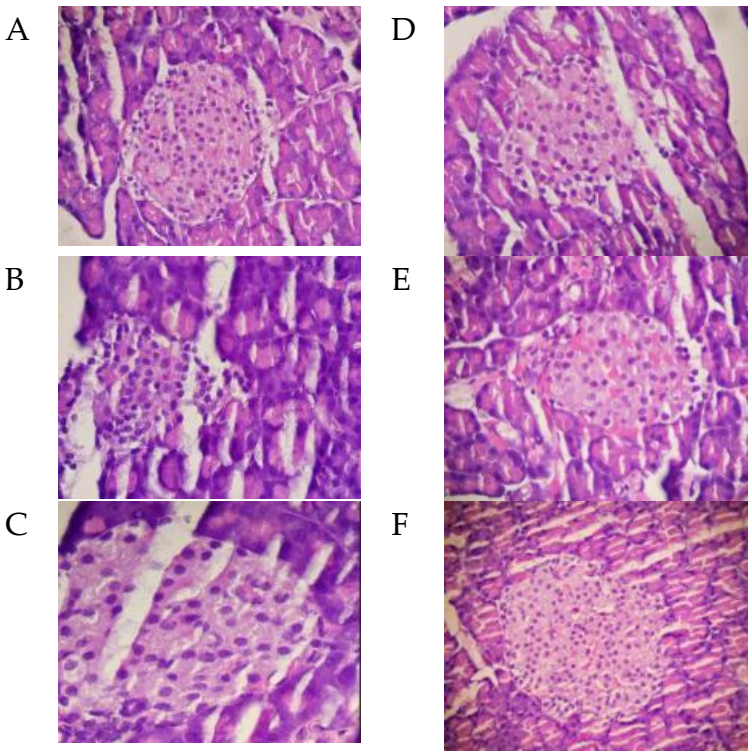

Figure 1. Histopathological examination results

As shown in Figure 1, panel A (normal group) exhibits a well-defined round-to-oval morphology of the islets of Langerhans with densely packed, uniformly distributed pancreatic cells. There is no evidence of necrosis, inflammation, or structural disorganization, establishing this as the reference for normal pancreatic architecture. This indicates intact and functional β-cell populations, essential for maintaining normoglycemia. In contrast,

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panels B, C, and D—which represent the negative control (aquadest + alloxan), positive control (glibencamide 0.65 mg/kg BW), and the 100 mg/kg BW extract group—show apparent pathological alterations. These include irregular islet contours, reduced cellular density, and scattered necrotic areas, with damage estimated to affect up to 25% of the islet area. This confirms the cytotoxic impact of alloxan, which selectively targets pancreatic β-cells by generating reactive oxygen species (ROS), leading to oxidative stress, DNA fragmentation, and eventual cellular apoptosis or necrosis[19,20].

Although the glibenclamide and low-dose extract groups show some preservation compared to the negative control, the histological damage remains significant, indicating limited protective or reparative capacity at this dose. Panel E (200 mg/kg BW) reveals a notably improved islet structure, with more compact cellular arrangements, better-defined boundaries, and fewer signs of necrosis or inflammatory infiltration. This suggests a partial restoration of pancreatic tissue, likely attributed to the enhanced antioxidant defense and modulation of inflammatory pathways afforded by the higher concentration of phytoconstituents in the extract [11].

Most strikingly, panel F (400 mg/kg BW) demonstrates a restored islet morphology closely resembling that of the normal group. The islets appear densely populated with minimal histological abnormalities, and the cellular architecture is preserved. This supports the hypothesis that bandotan extract at this dose provides a strong cytoprotective effect, potentially through the regeneration of β-cells and inhibition of alloxan-induced oxidative injury[21].

These morphological trends are consistent with the known pharmacodynamic properties of the bioactive constituents of *Ageratum conyzoides* L. Flavonoids act as potent antioxidants by neutralizing ROS, upregulating endogenous antioxidant enzymes (e.g., SOD, catalase), and stabilizing cellular membranes. Alkaloids and saponins have demonstrated anti-inflammatory and antidiabetic effects, including enhancement of insulin secretion and sensitivity. Additionally, triterpenoids/steroids may contribute to β-cell regeneration and repair of damaged tissues through modulation of cell signaling pathways involved in proliferation and apoptosis[22–24].

The dose-dependent improvements observed in islet integrity further support the therapeutic potential of Ageratum conyzoides as a natural alternative or complementary intervention for preserving pancreatic function in diabetes. These histopathological findings are in alignment with previous pharmacological reports but offer a novel visual and quantitative confirmation of tissue-level restoration in diabetic models [25].

Quantitative Analysis of Pancreatic Cell Damage

To quantitatively assess the degree of pancreatic damage, a histopathological scoring system was employed based on the severity of cellular degeneration and architectural disruption in the islets of Langerhans. The scoring data are presented

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in Table 2 and visually summarized in Figure 2.

Table 2. Mean Pancreatic Cell Damage Score in Alloxan-Induced Diabetic Rats

Group	*Mean*	*Standard deviation*	*Standar error of mean*
Normal (*aquadest*)	0.00	0.000	0.000
Negative Control (*aquadest* + alloxan)	1.25	0.500	0.250
Positive Control (glibenklamide + alloxan)	1.00	0.000	0.000
Dose 100 mg/kg BW + alloxan	1.00	0.000	0.000
Dose 200 mg/kg BW + alloxan	0.25	0.500	0.250
Dose 400 mg/kg BW alloxan	0.00	0.000	0.000

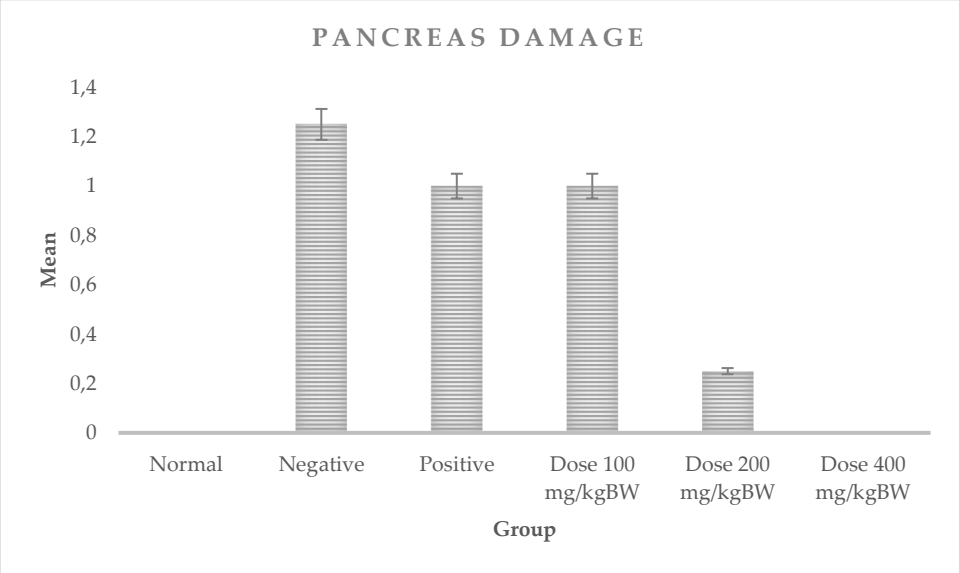

Figure 2. Mean score of pancreatic damage across treatment and control groups.

The negative control group (aquadest + alloxan) exhibited the highest mean damage score of 1.25 ± 0.50, which confirms the cytotoxicity of alloxan and validates its well-documented mechanism of β-cell destruction through oxidative stress. Alloxan selectively accumulates in pancreatic β-cells via the GLUT2 transporter, where it generates reactive oxygen species (ROS) and induces DNA fragmentation, mitochondrial dysfunction, and apoptotic signaling cascades. This culminates in severe structural damage to the islets of Langerhans and a marked reduction in insulin-producing cell populations. In contrast, the positive control group (glibencamide 0.65 mg/kg BW) and the 100 mg/kg BW bandotan extract group each showed a damage score of 1.00 ± 0.00, indicating partial protection against alloxan-induced injury, albeit with limited regenerative capacity. Glibenclamide, a sulfonylurea class antidiabetic drug, enhances insulin secretion by blocking ATP-sensitive potassium channels in β-cells but does not possess direct antioxidant or anti-inflammatory effects. The comparable score

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in the low-dose bandotan extract group suggests that at subtherapeutic levels, the phytochemicals may provide some antioxidant buffering, yet are insufficient to trigger meaningful cellular repair or regeneration[11,26].

In the 200 mg/kg BW group, the damage score dropped significantly to 0.25 ± 0.50, indicating substantial histological improvement, including better preservation of islet architecture, reduced necrosis, and restored cellular density. This intermediate dose appears to strike a balance between antioxidant defense and the activation of endogenous repair mechanisms. It reflects a threshold at which bioactive compounds such as flavonoids and saponins begin exerting more potent effects on reducing oxidative stress, modulating pro-inflammatory cytokines, and possibly stimulating β-cell neogenesis or proliferation[27].

The 400 mg/kg BW group displayed the most remarkable outcome with a score of 0.00 ± 0.00, identical to the normal group, suggesting complete histological protection. This reinforces the dose-dependent efficacy of *Ageratum conyzoides* L. extract in mitigating the deleterious effects of alloxan. The result supports the hypothesis that higher concentrations of the extract's constituents exert synergistic biological effects—neutralizing free radicals, inhibiting pro-apoptotic pathways (e.g., caspase-3 activation), and possibly enhancing the expression of insulin genes or β-cell transcription factors such as Pdx1[28].

The bar graph presented in Figure 8 provides a clear visual depiction of this trend, showing a stepwise decline in pancreatic damage scores from the negative control to the highest dose treatment group. All extract-treated groups and the glibenclamide group demonstrated lower damage scores than the untreated diabetic control, highlighting the therapeutic potential of the extract.

These findings are in line with earlier reports on the antidiabetic and tissue-protective properties of *Ageratum conyzoides*, yet they also extend current knowledge by offering quantitative histopathological evidence of its protective role in preserving pancreatic β-cell structure. The presence of flavonoids, alkaloids, triterpenoids, and saponins—as confirmed in the phytochemical screening—likely underpins these effects. These compounds are known to regulate oxidative stress via the Nrf2 pathway, inhibit inflammatory mediators like TNF-α and IL-1β, and reduce lipid peroxidation in pancreatic tissues.

CONCLUSION

The histopathological picture of the pancreas in alloxan-induced diabetic rats showed islets of Langerhans with oval-oblong shapes and <25% pancreatic cell damage. Treatment with *Ageratum conyzoides* L. (bandotan) leaf extract demonstrated the ability to repair pancreatic cell damage, with a dose of 400 mg/kg BW showing the most effective regenerative effect, restoring pancreatic architecture to near-normal conditions. These findings support the use of bandotan extract as a promising natural therapy for preserving β-cell integrity in diabetic conditions.

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