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Histological Analysis of Langerhans Islets and β-Cell Morphology in Diabetic Rats Treated with *Bischofia javanica* Nanoherbal

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder marked by hyperglycemia and β-cell damage. Standard therapies like metformin reduce blood glucose but rarely restore pancreatic structure. *Bischofia javanica* leaves, rich in flavonoids and phenolics, have traditional antidiabetic use with antioxidant and anti-inflammatory potential. This study evaluated the effects of nano herbal *B. javanica* on pancreatic histopathology in streptozotocin (STZ)-induced diabetic rats. Thirty male Wistar rats were divided into six groups: negative control (KN), positive control (KP), metformin 150 mg/kg BW (KS), and nano herbal B. javanica at 50 mg/kg BW (P1), 100 mg/kg BW (P2), and 200 mg/kg BW (P3). Pancreatic tissues were examined using hematoxylin-eosin staining and analyzed with the Pancreatic Injury Severity Score (ISS). Results showed that KP developed severe damage with the highest ISS (2.86), characterized by islet shrinkage, β-cell degeneration, insulitis, fibrosis, and vascular abnormalities. KS showed moderate improvement (ISS 1.71), while nano herbal treatment groups exhibited dose-dependent recovery. P3 (200 mg/kg BW) achieved near-normal morphology with the lowest ISS (0.71), demonstrating superior effects compared to KS. These findings suggest that nano herbal *B. javanica* protects and regenerates pancreatic β-cells through antioxidant and anti-inflammatory mechanisms, while nano formulation enhances bioavailability and therapeutic efficacy of its active compounds.

Keywords: *Bischofia javanica*, diabetes mellitus, pancreas, histology, nanoherbal

ABSTRACT

Diabetes melitus (DM) adalah gangguan metabolik kronis yang ditandai dengan hiperglikemia dan kerusakan sel β. Terapi standar seperti metformin dapat menurunkan kadar glukosa darah, tetapi jarang mampu memulihkan struktur pankreas. Daun Bischofia javanica, yang kaya akan flavonoid dan fenolik, secara tradisional digunakan sebagai obat antidiabetes dan memiliki potensi antioksidan serta antiinflamasi. Penelitian ini mengevaluasi efek nanoherbal B. javanica terhadap histopatologi pankreas pada tikus diabetes yang diinduksi streptozotocin (STZ). Sebanyak 30 ekor tikus jantan Wistar dibagi menjadi enam kelompok: kontrol negatif (KN), kontrol positif (KP), metformin 150 mg/kg bb (KS), serta nanoherbal B. javanica dengan dosis 50 mg/kg bb (P1), 100 mg/kg bb (P2), dan 200 mg/kg bb (P3). Jaringan pankreas diperiksa dengan pewarnaan hematoksilin-eosin, kemudian dianalisis menggunakan Indeks Skor Pankreas (ISS). Hasil menunjukkan bahwa KP mengalami kerusakan berat dengan ISS tertinggi (2,86), ditandai penyusutan pulau Langerhans, degenerasi sel β, insulitis, fibrosis, dan kelainan vaskular. KS menunjukkan perbaikan sedang (ISS 1,71), sedangkan kelompok perlakuan nanoherbal

memperlihatkan perbaikan bertahap sesuai dosis. P3 (200 mg/kg bb) menghasilkan morfologi mendekati normal dengan ISS terendah (0,71), lebih baik dibanding KS. Temuan ini menegaskan bahwa nanoherbal B. javanica berpotensi melindungi dan meregenerasi sel β pankreas melalui mekanisme antioksidan dan antiinflamasi, serta bahwa formulasi nano meningkatkan bioavailabilitas dan efektivitas senyawa aktifnya.
Keyword: *Bischofia javanica, diabetes melitus, pankreas, histologi, nanoherbal*

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder with a global prevalence that continues to increase, characterized by hyperglycemia due to impaired insulin secretion or action. One of the main target organs in the pathogenesis of DM is the pancreas, particularly the Langerhans islets containing β-cells as insulin-producing cells. Histopathological alterations commonly observed include a reduction in the number and size of islets, β-cell atrophy, vacuolization, pyknosis, lymphocytic infiltration (insulitis), stromal fibrosis, and vascular changes, all of which contribute to the decline in insulin secretory capacity [1].

Standard therapy such as metformin has been widely used to control blood glucose levels; however, its long-term use is often accompanied by side effects and does not fully restore the histological integrity of the pancreas. Therefore, the search for alternative therapeutic agents derived from natural products that are safer and more effective has become an important focus of current research. One of the promising candidates is *Bischofia javanica* (Sikkam leaves), traditionally utilized in the treatment of various ailments and shown to contain bioactive compounds such as quercetin and gallic acid. Quercetin has been reported to suppress hyperglycemia by inhibiting active glucose transport, while gallic acid exhibits antidiabetic activity primarily through its antioxidant properties [1, 2].

Several studies have demonstrated the antidiabetic potential of *B. javanica*. Ethanol extracts of B. javanica leaves significantly enhanced insulin expression and reduced the degree of insulitis in the pancreatic histology of diabetic rats, with higher doses (900 mg/kg BW) yielding effects comparable to glibenclamide [1, 3]. Likewise, another study reported that *B. javanica* leaf extract reduced blood glucose levels and improved Langerhans islet histology in alloxan-induced diabetic rats, with the most effective antidiabetic activity observed at 900 mg/kg BW [3]. In addition, methanolic extracts of *B. javanica* stem bark demonstrated antidiabetic activity attributed to phenolic and flavonoid contents [4], while decoction preparations of the bark improved pancreatic histology by increasing the diameter of Langerhans islets [5]

The development of nanoherbal formulations represents a novel strategy to improve the bioavailability of active compounds from *B. javanica*. Nanoherbal Sikkam leaves (NSL) were reported to have a particle size of approximately 188 nm with very strong antioxidant activity (IC50 28.24 µg/mL), and provided superior physiological effects compared to ethanol extracts, particularly in hematological, liver biochemical, and urinary electrolyte parameters. Chronic toxicity studies further revealed that moderate doses of nanoherbal B. javanica are safe and enhance physiological functions, whereas higher doses may induce hepatic and multi-organ damage [6]. Acute toxicity testing also confirmed its relative safety, with an LD50 value of 12.6 g/kg BW [7].

Moreover, nanoherbal *B. javanica* has been evaluated in cancer models, particularly oral squamous cell carcinoma (OSCC). A combination of nanoherbal B. javanica leaves and *Phaleria macrocarpa* fruits significantly reduced hematological and lipid profile disturbances, while improving hepatic and renal function in benzo[a]pyrene-induced OSCC rats [8]. These findings underscore the multifunctional therapeutic potential of B. javanica as an antioxidant, antidiabetic, and anticancer agent.

Based on these considerations, the present study aimed to evaluate the effects of nanoherbal *B. javanica* leaves on the histopathological repair of pancreatic tissue in diabetic rats, focusing on Langerhans islet number and size, β-cell morphology, insulitis, stromal fibrosis, vascularization, and exocrine tissue alterations.

2. Methods

2.1 Experimental Animal

Male *Rattus norvegicus* (Wistar strain), aged 8–10 weeks and weighing 180–220 g, were used in this study. The animals were acclimatized for 7 days under controlled laboratory conditions (temperature 22–25 °C, 12 h light/dark cycle, and ad libitum access to food and water). All experimental procedures were conducted in compliance with institutional ethical guidelines for animal research.

2.2 Induction od Diabetes

Diabetes mellitus was induced in rats through intraperitoneal injection of streptozotocin (STZ) at a dose of 50 mg/kg body weight, dissolved in 0.1 M citrate buffer (pH 4.5). Blood glucose levels were measured 72 h post-injection using a glucometer. Rats with fasting blood glucose levels above 200 mg/dL were considered diabetic and included in the study.

2.3 Preparation of Nanoherbal Treatment

Fresh leaves of *Bischofia javanica* were collected, washed, shade-dried, and ground into a fine powder. The powder was processed into nanosized particles using the High-Energy Milling (HEM) method. The particle size distribution was confirmed by Particle Size Analyzer (PSA), and morphology was examined using Scanning Electron Microscopy (SEM) at the earlier study [9].

2.4 Experimental Design

The diabetic rats were randomly divided into the following groups:

Table 1. Group and treatment

Group	Description
KN	Negative control (healthy rats without induction or treatment)
KP	Positive control (diabetic rats without treatment)
KS	Standard treatment (diabetic rats treated with Metformin 150 mg/kg BW)
P1	Diabetic rats treated with nanoherbal *Bischofia javanica* leaves 50 mg/kg BW
P2	Diabetic rats treated with nanoherbal *Bischofia javanica* leaves 100 mg/kg BW
P3	Diabetic rats treated with nanoherbal *Bischofia javanica* leaves 200 mg/kg BW

2.5 Histological Analysis

At the end of the treatment period, rats were sacrificed under anesthesia, and pancreatic tissues were collected. The samples were fixed in 10% formalin, dehydrated, embedded in paraffin, sectioned at 5 μm thickness, and stained with hematoxylin and eosin (H&E).

2.6 Microscopic Examination

The morphology of pancreatic islets (islets of Langerhans) and β-cells was evaluated under a light microscope. Parameters such as islet diameter, cellular distribution, and degenerative changes in β-cells were analyzed. Digital photomicrographs were captured for documentation and quantitative analysis.

2.7 Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical differences among groups were analyzed using one-way ANOVA followed by Tukey's post hoc test. A p-value < 0.05 was considered statistically significant.

3. Result and Discussion

3.1 Morphological Evaluation of Pancreatic Islets

Histopathological examination of pancreatic tissues across experimental groups revealed distinct morphological differences in the islets of Langerhans and β-cells, reflecting the impact of diabetes induction and subsequent treatments. In the negative control group (KN), which consisted of healthy rats without induction, the pancreatic tissue appeared normal. The islets of Langerhans were intact, with well-defined architecture and densely packed β-cells. No signs of vacuolization, necrosis, inflammatory infiltration, or vascular abnormalities were observed. These findings confirm that the baseline pancreatic histology was preserved in the absence of diabetic induction, thus serving as a reference for assessing pathological changes in other groups.

In the positive control group (KP), which represented diabetic rats without treatment, severe structural damage was observed. The islets of Langerhans appeared markedly shrunken with irregular boundaries and extensive β-cell degeneration. Cytoplasmic vacuolization, pyknotic nuclei, and disorganization of cell clusters were prominent. Inflammatory cell infiltration and vascular congestion were also evident, indicating pronounced tissue injury (Table 2). These alterations confirm the destructive effects of hyperglycemia on pancreatic tissue, consistent with previous reports that chronic oxidative stress and inflammatory responses play a central role in β-cell loss in diabetes [1, 5]. The standard treatment group (KS, metformin 150 mg/kgBW)

showed moderate improvement compared to KP. The islets were relatively preserved, with reduced necrosis and fewer inflammatory cells. β-cell morphology appeared more organized, though mild vacuolization and occasional cell loss were still observed. The histopathological scoring (ISS = 1.71) indicated a moderate protective effect (Table 3). This supports the known antidiabetic mechanism of metformin, which enhances insulin sensitivity and exerts antioxidant effects, thereby attenuating β-cell damage [4].

The nanoherbal treatment groups demonstrated a clear dose-dependent improvement in pancreatic histology. At the lowest dose, P1 (50 mg/kgBW) showed partial protective effects, characterized by reduced but still noticeable β-cell vacuolization and mild infiltration of inflammatory cells. The islets of Langerhans in this group remained relatively small and irregular in shape, suggesting limited regenerative activity. In contrast, P2 (100 mg/kgBW) exhibited more substantial restoration, as reflected by larger and better-defined islets with denser β-cell populations and markedly reduced vacuolization. Inflammatory cell infiltration was minimal compared to P1, and vascular structures appeared healthier, indicating that the higher dose enhanced the capacity to suppress oxidative and inflammatory stress while supporting β-cell survival (Figure 1). The most remarkable improvement was observed in P3 (200 mg/kgBW), where the pancreatic architecture was nearly normal. The islets appeared well-preserved in size and structure, with clearly defined cell boundaries, compact endocrine cell clusters, and minimal degenerative changes. No inflammatory infiltration was observed, and vascular integrity remained intact. These histological improvements were consistent with the lowest ISS score (0.71) among treatment groups, suggesting that high-dose nanoherbal B. javanica exerted superior protective effects, even compared to metformin (Table 3). The therapeutic efficacy at this dose is likely mediated by the synergistic action of bioactive compounds such as flavonoids, phenolics, and triterpenoids, which function as potent antioxidants, anti-inflammatory agents, and promoters of β-cell regeneration [5, 10].

Table 2. Histopathological Evaluation of Pancreatic Tissue in Different Experimental Groups

Parameter	KN	KP	KS	P1 (50)	P2 (100)	P3 (200)
Islets of Langerhans – number/size	0.00 ± 0.00	3.00 ± 0.29	2.00 ± 0.20	2.00 ± 0.25	1.00 ± 0.10	1.00 ± 0.15
Islet cell morphology (atrophy/vacuolization/pyknosis)	0.00 ± 0.00	3.00 ± 0.31	2.00 ± 0.18	2.00 ± 0.22	1.00 ± 0.10	1.00 ± 0.12
Insulitis (lymphocyte infiltration)	0.00 ± 0.00	3.00 ± 0.27	1.00 ± 0.15	2.00 ± 0.20	1.00 ± 0.08	0.00 ± 0.00
Stromal fibrosis of the islets	0.00 ± 0.00	3.00 ± 0.33	2.00 ± 0.22	2.00 ± 0.20	1.00 ± 0.10	1.00 ± 0.14
Changes in exocrine tissue	0.00 ± 0.00	2.00 ± 0.20	1.00 ± 0.10	1.00 ± 0.12	1.00 ± 0.10	0.00 ± 0.00
Vascularization (capillary thickening/hyalinization)	0.00 ± 0.00	3.00 ± 0.30	2.00 ± 0.25	2.00 ± 0.22	1.00 ± 0.10	1.00 ± 0.12
Necrosis/Apoptosis in the islets	0.00 ± 0.00	3.00 ± 0.28	2.00 ± 0.20	2.00 ± 0.25	1.00 ± 0.10	1.00 ± 0.15

0 = normal, 1 = mild, 2 = moderate, 3 = severe

Table 3. Total Histopathological Score and Pancreatic Injury Severity Score (ISS) in Experimental Groups

Group	Total Score	ISS
KN	0.00 ± 0.00	0.00 ± 0.00
KP	20.00 ± 1.20	2.86 ± 0.25
KS (Metformin 150)	12.00 ± 0.95	1.71 ± 0.18
P1 (50)	13.00 ± 1.05	1.86 ± 0.20
P2 (100)	7.00 ± 0.80	1.00 ± 0.10
P3 (200)	5.00 ± 0.70	0.71 ± 0.12

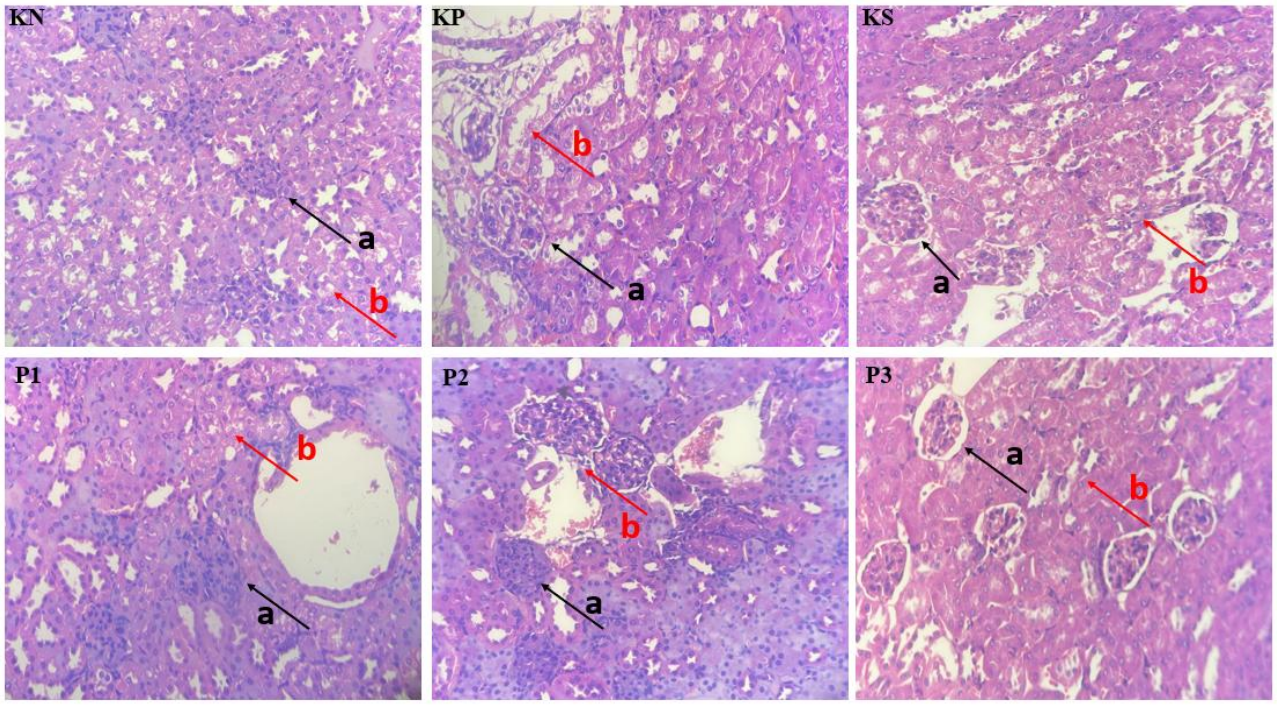

Figure 1. Histological Analysis of Pancreatic Tissue under Different Conditions. a: Islet of Langerhans; b: Lymphocyte infiltration

Furthermore, the nanoformulation itself appears to enhance the efficacy of *B. javanica*. Nano herbal technology improves solubility, cellular penetration, and bioavailability of phytochemicals, thereby amplifying their physiological and pharmacological effects compared to crude ethanol extracts[1-3]. Nonetheless, toxicity studies have also highlighted the importance of dose regulation, since excessively high concentrations of nanoformulated B. javanica can cause hepatic and renal alterations [7]. This underscores the necessity of balancing therapeutic efficacy and safety when applying nano herbal formulations.

Overall, the results demonstrate that nanoherbal *B. javanica* improves pancreatic histopathology in a dose-dependent manner, with P3 achieving near-normal morphology. This outcome not only supports the ethnomedicinal use of *B. javanica* as an antidiabetic agent but also highlights the promise of nanoformulation technology in enhancing the therapeutic potency of herbal medicines for diabetes

3.2 Histological Quantitative Assessment of Pancreatic Histology

The difference between KN and KP highlights the pathological consequences of uncontrolled diabetes on pancreatic architecture. The findings indicate that hyperglycemia and oxidative stress contribute to β-cell necrosis, insulitis, and fibrosis, which are characteristic hallmarks of diabetic pancreatic injury. Similar results have been reported in previous studies, where uncontrolled diabetes led to islet shrinkage, β-cell apoptosis, and increased inflammatory infiltration [11].

This baseline contrast also provides a foundation to evaluate the therapeutic effects of treatments. Compared to KP, both metformin (KS) and nanoherbal B. javanica (P1–P3) showed improvements (Table 2), indicating partial or significant restoration of pancreatic histology. The dose-dependent recovery observed in nanoherbal groups further supports the role of phytochemical antioxidants and anti-inflammatory agents in protecting β-cells [12, 13]. Quantitative analysis using the Injury Severity Score (ISS) revealed clear differences among groups. The KN group maintained an ISS of 0, confirming the absence of histological abnormalities. In contrast, KP exhibited the highest ISS (2.86), indicating severe pancreatic damage characterized by significant islet loss, β-cell degeneration, extensive insulitis, fibrosis, vascular changes, and necrosis. These findings validate the destructive impact of persistent hyperglycemia on pancreatic integrity (Figure 1). The KS group (metformin 150 mg/kgBW) demonstrated a lower ISS of 1.71, consistent with moderate pancreatic protection (Table 3). Histologically, this improvement was associated with partial preservation of islet size and reduced inflammatory infiltration, although mild vacuolization and fibrosis remained evident. These results are aligned with the known pharmacological profile of metformin, which mitigates oxidative stress and improves insulin sensitivity, thereby reducing but not fully preventing β-cell damage.

In the nanoherbal treatment groups, progressive improvements were observed in line with increasing

dosage. P1 (50 mg/kgBW) showed an ISS of 1.86, which, although close to KS, suggested only partial restoration. The islets were irregular and moderately damaged, and inflammatory infiltration persisted, reflecting limited efficacy at this lower dose. P2 (100 mg/kgBW) yielded a markedly improved ISS of 1.00, corresponding to only mild pancreatic injury. This group demonstrated larger and more defined islets, minimal vacuolization, and reduced inflammatory activity, highlighting enhanced protective effects. P3 (200 mg/kgBW) exhibited the lowest ISS among all treatment groups (0.71), approaching the normal range. The nearly intact morphology of the islets, absence of insulitis, and preservation of vascular and exocrine tissue structure indicated superior therapeutic efficacy. The trend observed across P1–P3 clearly demonstrates a dose-dependent effect of nanoherbal B. javanica. At higher doses, the formulation was able to attenuate β-cell degeneration, suppress inflammatory processes, and preserve islet integrity more effectively than metformin. This finding is in agreement with pharmacological evidence that methanol and ethanol extracts of B. javanica possess strong antioxidant, anti-inflammatory, and antibacterial activities, mediated by compounds such as gallic acid, kaempferol, quercetin, and β-sitosterol [11-13]. Moreover, the ethnobotanical significance of B. javanica in Simalungun and other Asian communities underscores its long-standing use in treating metabolic and inflammatory disorders [14].

Notably, advances in nanotechnology also support the improved therapeutic potential of B. javanica. Nanoformulation increases bioavailability, cellular penetration, and stability of phytochemicals, thereby enhancing their physiological efficacy. Recent innovations, such as the use of B. javanica extract in nanoparticle and hydrogel systems, have demonstrated potent antimicrobial, wound-healing, and regenerative properties [15], reinforcing the translational promise of nanoherbal *B. javanica* in diabetes therapy. Taken together, the histological improvements observed in P1–P3 groups, particularly at high doses, provide strong experimental support for the medicinal value of *B. javanica* and highlight the synergistic contribution of ethnomedicine, bioactive phytochemicals, and nanotechnology in advancing alternative therapeutic strategies for diabetes management.

4. Conclusion

This study demonstrates that nanoherbal *Bischofia javanica* significantly improves pancreatic histology in diabetic rats in a dose-dependent manner. While the positive control group (KP) exhibited severe islet shrinkage, β-cell degeneration, insulitis, fibrosis, and vascular abnormalities, treatment with metformin (KS) and nanoherbal *B. javanica* (P1–P3) showed progressive restoration of pancreatic integrity. Notably, the highest dose (P3, 200 mg/kgBW) achieved near-normal morphology with the lowest ISS score (0.71), surpassing the protective effects of metformin. These findings confirm that the therapeutic activity of B. javanica is mediated by its bioactive phytochemicals, including flavonoids, phenolics, and triterpenoids, which act as antioxidants and anti-inflammatory agents to protect and regenerate β-cells. Moreover, nanoformulation technology enhances the bioavailability and efficacy of these compounds, supporting its potential as an adjunct or alternative strategy for diabetes management.

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6. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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