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Original Article

In vivo study of celery (*Apium graveolens* L) extract for regenerating pancreatic β-cell

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A B S T R A C T

Background: The celery plant (*Apium graveolens* L.) is a widely distributed herbal plant globally known for being a significant source of natural active products, including phenolic compounds and antioxidants demonstrating antidiabetic activity. Previous research findings have indicated the impact of celery leaf extract on reducing blood glucose levels. However, up to now, there is a dearth of research investigating the potential effect of celery leaf extract on the regeneration of pancreatic beta cells in mice with diabetes models.

Objective: This study aims to determine the effect of the ethanol extract of celery leaves on the number of pancreatic cells in Streptozotocin (STZ)-induced mice.

Method: This research method uses a randomized controlled group posttest only design. Experimental animals were divided into five groups, including a group of experimental animals in a healthy condition, the group with hyperglycemia, hyperglycemia group with celery extract at 200 mg/kg BW, hyperglycemia group with celery extract at 400 mg/kg, and hyperglycemia group with extract celery is 800 mg/kg BW. Termination was performed on day 60 after therapy and pancreas hematoxylin and eosin staining. They are counting the number of cells with a photo slide with 400x magnification in 5 fields of view—statistical analysis using One-Way ANOVA.

Results: The study revealed that celery extract could increase the number of pancreatic cells compared to the control group (P<0.002). Notably, the highest increase in pancreatic cell count was observed in the group administered with 400 mg/BW of celery extract.

Conclusion: Celery leaf extract effectively increased the number of beta cells in vivo.

INTRODUCTION

The hormone insulin plays a crucial role in carbohydrate metabolism, produced by pancreatic beta cells. Impaired insulin secretion, insulin action, or both can disrupt glucose metabolism, resulting in hyperglycemia. Clinically, hyperglycemia serves as an indicative sign of diabetes. As of the end of 2021, the global prevalence of diabetes, as reported by the International Diabetes Federation (IDF), stands at 537 million people. This number is projected to rise, reaching 643 million by 2030 and 783 million by 2045.[1] In Indonesia, the prevalence of diabetes is notable, with the country ranking among the top five globally in terms of incidence, affecting 19.4 million individuals out of a population of 179 million between the ages of 20 and 79 years. This figure is expected to escalate to 28.6 million by 2045.[2]

Diabetes mellitus poses a significant global public health challenge, contributing to both social and economic burdens.[3] As a chronic metabolic disease, diabetes mellitus carries a lifelong risk and operates as a silent yet potent threat, capable of causing premature death.[4] Uncontrolled diabetes mellitus can lead to various comorbidities and complications. Research findings from 2017 reveal that microvascular complications were the most common chronic issues in diabetes mellitus patients, accounting for 57%. Predominant complications included diabetic neuropathy (45.6%), diabetic nephropathy (33.7%), and diabetic retinopathy (20.7%). Macrovascular complications

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accounted for 43%, with diabetic foot (29.9%), coronary heart disease (27.8%), and cerebrovascular disease (19.4%) being the most prevalent.[5] Globally, diabetes-related deaths or deaths due to its complications amounted to 6.7 million people in 2021.[1]

The prevention and treatment of diabetes mellitus (DM) are imperative to manage the increasing number of individuals affected by this condition. The fundamental approach to therapy for diabetes patients involves controlling blood glucose levels through lifestyle modifications, such as diet and physical activity,[6] alongside the regular use of antidiabetic drugs.[7] These drugs enhance insulin production, increase cell sensitivity to insulin, and inhibit glucose production by the liver.[8] However, the prolonged use of antidiabetic drugs carries economic costs for DM patients and the national health care system.[9] Additionally, extended use of these medications may lead to various side effects and complications, including bone issues, weight gain, and cardiovascular disease.[10] Hence, there is a pressing need to explore and develop new alternative antidiabetic drugs that specifically target pancreatic β cells to prevent or treat diabetes mellitus.

The celery plant (*Apium graveolens* L.) is a widely distributed herbal plant globally known for being a significant source of natural active products, including phenolic compounds and antioxidants that have demonstrated antidiabetic activity. Previous research findings have indicated the impact of celery leaf extract on reducing blood glucose levels.[11] However, up to now, there is a dearth of research investigating the potential effect of celery leaf extract on the regeneration of pancreatic beta cells in mice with diabetes models. Understanding the potential regenerative effects of celery leaf extract on pancreatic beta cells could offer valuable insights into its therapeutic properties for diabetes management. Future research endeavors in this area could contribute to expanding our knowledge of the comprehensive impact of celery leaf extract on diabetes and its potential role in promoting the regeneration of pancreatic beta cells, a crucial element in insulin production. The primary objective of this study is to assess the effect of the extract of celery leaves on the number of pancreatic β-cell in Streptozotocin (STZ)-induced mice.

METHOD

Study Design

This is an experimental study with a randomized posttest-only controlled group design.

Study Site

This research was conducted in the Pharmacology Laboratory of the Faculty of Medicine, Brawijaya University, Malang.

Materials

The materials used in this research included 500 grams of celery leaf powder and 25 male rats of the Wistar strain, aged 2-3 months and weighing 20-30 grams each.[12] he equipment comprised a blender, distilled water, Erlenmeyer glass, 96% Ethanol, evaporator, 96% alcohol, physiological NaCl 0.9%, thermometer, rat cage, rat food, scales, syringe, STZ, Citrate buffer pH 4.5, glucometer, rubber-tipped tube, scalpel, rod, scalpel blade, hand glove, tissue, formalin, preparations, Hematoxylin-Eosin (H&E) staining, and a microscope OLYMPUS BX51 series.[13]

Plant Extraction Process

Celery leaves were sourced from the Medical Materials Department, with selected leaves ranging from light green to dark green. Subsequently, the leaves were thoroughly washed with running water to ensure cleanliness. Following this, the leaves were air-dried at room temperature to prevent damage to the substances present in celery leaves caused by sunlight. Once dried, the leaves were grinding using a blender, resulting in a 500-gram powder of celery leaves. The next step involved placing the 500 grams of celery leaf powder into a 1-liter Erlenmeyer glass. The powder was then immersed in ethanol until reaching a volume of 1000 ml. The celery leaf powder and ethanol mixture were thoroughly shaken and left to stand for 24 hours to allow for evaporation.[14] After this period, the top layer of the ethanol mixture containing the active substances was carefully extracted and transferred into a 1-liter evaporation flask. The flask was positioned on the evaporator during the evaporation process, and the water bath was filled to capacity. All equipment, including the rotary evaporator and water bath heater, was set up, with the temperature adjusted to a range of 70°C to 80°C.[15] The entire apparatus was then connected to a power source.

In Vivo Procedure

Animal Preparation

The experimental animals used were male BALB/c mice, aged 2-3 months, weighing 20-30 grams, totaling 25 animals. Each group consisted of 5 experimental animals. All treatments administered to the experimental animals received prior approval from the Health Research Ethics Commission at the Faculty of Medicine, University of Brawijaya. Research animals were acclimated to laboratory cages to ensure their health and readiness for treatment. The experimental animals were then divided into five groups. The control group comprised two subgroups: the first consisted of mice in a healthy condition (N), and the second included mice in a hyperglycemic condition without receiving celery leaf extract (Po). Treatment Group 1 (P1) involved mice receiving 200 mg/kg BW of celery leaf extract, Treatment Group 2 (P2) included mice receiving 400 mg/kg BW of celery leaf extract, and Treatment Group 3

(P3) comprised mice receiving celery leaf extract at 800 mg/kg BW.[16]

Experimental Procedure

Mice were induced through intraperitoneal injection with a single dose of STZ at 70 mg/kg BW, dissolved in a 0.1 M citrate solvent at pH 4.5. Prior to injection, the mice were fasted for 12 hours.[17] Seven days post the STZ injection, glucose levels were assessed using a digital glucometer. Hyperglycemia was defined as blood glucose levels exceeding 200 mg/dL. Celery extract therapy was administered through a rubber tip tube with dosages of 200 mg/kg BW for Group I, 400 mg/kg BW for Group II, and 800 mg/kg BW for Group III. The administration positioned the mice with their mouths facing upwards, securing them by holding on to the scalp. Subsequently, the probe was inserted through the mouth, and the celery leaf extract was injected.

Histopathology Analysis

Pancreatic tissue samples were collected post-surgery and immersed in a 10% formalin fixative solution. Subsequently, pancreatic tissue preparations were created using Hematoxylin and Eosin (H&E) staining. Microscopic examinations were conducted with a photomicroscope at 400x magnification to quantify the number of pancreatic beta cells.[18]

Statistical Analysis

Data analysis was conducted using descriptive methods, with cell shape data and β cell number data expressed as mean ± SD. Multivariate analysis was performed using the One-Way ANOVA test.

Ethical Consideration

This research has been approved by the research ethics committee of Medical Faculty, University of Brawijaya, No.015/EC/KEPK-S1_PSIK/ 01/2005.

RESULTS

Histopathological Features of Pancreatic β cells

Histological observations on pancreatic preparations from normal mice and pre-treated diabetic mice revealed distinct structures, as depicted in Figures 1 A and B. Based on the observation results at 400x magnification, Langerhans islets were discernible in the pancreas of normal mice. The islet composition appeared compact and contained numerous beta cells. In contrast, the examination of the STZ-induced pancreas at 400x magnification indicated that the exocrine components of the pancreas underwent necrosis, and there was a significant reduction in the number of beta cells. Histological observations on rat preparations treated with dosages of 200 mg/kg BW for Group I, 400 mg/kg BW for Group II, and 800 mg/kg BW for Group III, as depicted in Figures 1 B, C, and D, demonstrated signs of beta cell regeneration. The islet composition appeared compact and contained a higher number of beta cells compared to the pre-treatment group of diabetic mice.

Pancreatic β cells Count

Table 1 reveals significant differences in the groups' mean number of pancreatic beta cells. The negative control group (N) exhibited the highest mean number of pancreatic beta cells, recording a mean of 71.44 ± 8.560. In contrast, the positive control group (P0) displayed the lowest mean number of pancreatic beta cells, precisely 47.60 ± 11.788. Comparing the mean number of beta cells from the three treatment groups to the positive control group (P0), it is evident that the three treatment groups collectively exhibit a higher number. Treatment II (P2) stands out among the treatment groups with the highest mean number of beta cells, registering at 68.92 ± 9.049. This surpasses the mean values for Treatment I (P1) and Treatment III (P3), which are 65.56 ± 5.802 and 63.64 ± 5.324, respectively.

The results of the multivariate analysis in Table 2 highlight significant differences among the experimental groups. Post-hoc testing revealed that group P0 (subset 1) was placed in a different subset column from groups N (subset 2), P1 (subset 2), P2 (subset 2), and P3 (subset 2), indicating a significant difference between the control group and the treatment group (p = 0.002). Consequently, the administration of celery leaf extract significantly increases the number of pancreatic beta cells.

Table 1. The Mean Number of Pancreatic β Cells varied Across the Study Groups

Group	Number of Cells Per Five Fields of View
	Mean ± SD
Negative Control (N)	71,44 ± 8,560
Positive Control (Po)	47,60 ± 11,788
Treatment I (P1)	65,56 ± 5,802
Treatment II (P2)	68,92 ± 9,049
Treatment III (P3)	63,64 ± 5,324

Table 2. Results of Multivariate Analysis of Homogeneous Subset Number of Pancreatic β cells

Treatment	Subset for alpha= 0.05	
	1	2
Po		
P3		63.64
P1		65.56
P2		68.92
N		71.44
Sig	1.000	0.002

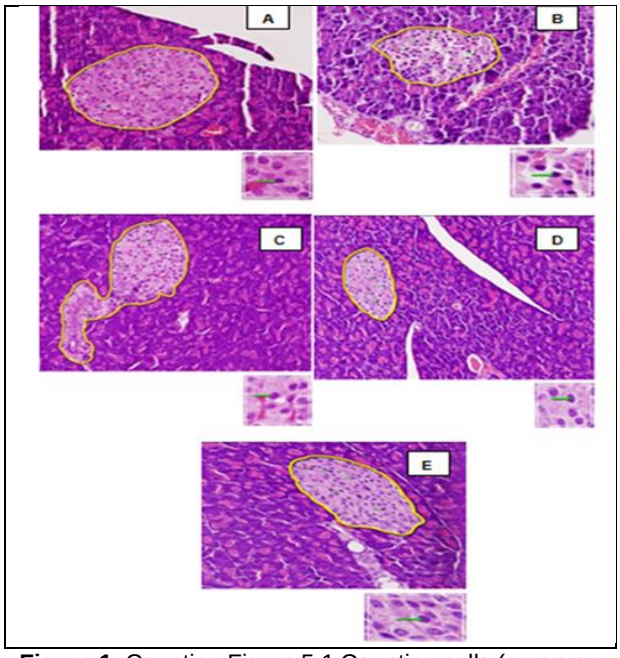

Figure 1. Counting Figure 5.1 Counting cells (green arrows) with 400x magnification H&E staining in the negative group (A), positive group (B), treatment group I (C), treatment group II (D), and treatment group III (E)

DISCUSSION

The histological observations of pancreatic beta cells indicate a difference in the number of pancreatic beta cells between the positive control group (P0) and the negative control group (N). The pancreatic cell damage observed in the positive control group (P0) was attributed to STZ administration. STZ increases oxidative and cytotoxic stress on pancreatic islets, impacting insulin release. STZ causes impaired glucose oxidation, decreased insulin biosynthesis and secretion, and the production of ROS, contributing to DNA fragmentation and cellular damage.[19] This excess ROS elevates oxidative stress and damages pancreatic beta cells. Changes in blood glucose levels reflect abnormalities in cell function and structure. Hyperglycemia intensifies superoxide production in mitochondria, potentially activating Uncoupling Protein-2 (UCP-2) and leading to beta cell apoptosis.[20] Elevated blood glucose levels increase the formation of free radicals through glucose metabolism pathways, such as glucose autooxidation, methylglyoxal formation, and oxidative phosphorylation.[21]

The study results revealed a significant difference in the number of beta cells observed between the control and treatment groups receiving celery leaf extract. Experimental animals in the treatment groups (P1, P2, and P3) exhibited more beta cells than the positive control group. This difference is likely attributed to the administration of leaf extract, creating conditions conducive to normal beta cell repair processes. Under normal conditions, homeostasis occurs, where the body's internal environment maintains a constant state.[22] Therefore, it can be concluded that administering celery leaf extract at 200 mg/kg BW, 400 mg/kg BW, and 800 mg/kg BW still positively affects and maintains homeostatic conditions.

The treatment group (P2), administered celery leaf extract at a 400 mg/kg BW dose, exhibited the highest mean regeneration result, 68.92 ± 9.049. Celery leaves contain several phytochemicals, including flavonoids, saponins, tannins, and polyphenols.[23] Flavonoids such as apigenin, choline, and phytosterols, known for their antioxidant and anti-inflammatory effects, are believed to play a role in the regeneration of pancreatic beta cells responsible for insulin production.[24] Numerous studies have demonstrated the hypoglycemic effects of flavonoids through various mechanisms, such as reducing glucose absorption, enhancing glucose tolerance, and facilitating the regeneration of damaged pancreatic beta cells.[25-27] Research conducted on hyperglycemic mice revealed a positive impact on reducing blood glucose levels by administering ethanol extract from moringa bark.[28] The combined action of flavonoid and alkaloid compounds within the pancreas works through an intra-pancreatic mechanism, aiming to repair and regenerate damaged pancreatic β-cells while providing protective effects to prevent further damage.[29]

The oral administration of celery leaf extract positively impacted the number of cells due to the high flavonoid content in celery leaves.[30] Variations in cell numbers between groups may be influenced by the presence of flavonoid compounds. Wet celery leaves contain approximately 139 mg/kg of apigenin and 23 mg/kg of luteolin.[31] Flavonoids like apigenin and luteolin possess antioxidant effects.[32] The antioxidant properties of celery leaves are beneficial in inhibiting the increase in reactive oxygen species (ROS), thereby preventing cell damage.[33] Flavonoids enhance the activity of the antioxidant protection system, beneficially affecting pathological changes caused by ROS and maintaining the integrity of pancreatic cells.[34] Flavonoids act as antioxidants and protect against free radical damage through two mechanisms.[35] The first mechanism involves donating hydrogen ions to form more stable oxidizing compounds.[29] The second mechanism is direct free radical scavenging. Flavonoids also bind free radicals, inhibit lipid peroxidation, prevent oxidative stress due to STZ administration, and protect beta cells, resulting in increased insulin secretion and decreased blood glucose.[36] Flavonoids enhance antioxidant enzyme levels, such as superoxide dismutase (SOD) and catalase (CAT), countering the decrease in these enzymes as blood glucose levels rise.[37]

Several studies have highlighted the potential role of flavonoids in Bajakah wood, orange peel, and dragon fruit in regenerating pancreatic beta cells, increasing insulin production, and regulating blood glucose levels.[38-40] However,

limited research has specifically addressed the role of flavonoids from celery leaves in pancreatic beta-cell regeneration. Nonetheless, other studies indicate that the ethanol extract of celery leaves can enhance the number of pancreatic beta cells in mice.[22] From the available evidence, it can be inferred that flavonoids present in celery leaves may contribute to the regeneration of pancreatic beta cells. However, it is essential to emphasize that further research is necessary to confirm and expand our understanding of the specific role of celery leaf flavonoids in this process.

CONCLUSIONS AND RECOMMENDATION

Oral administration of celery leaf extract proved effective in increasing the number of beta cells in mice induced by Streptozotocin. The most effective dose of celery leaf extract was found to be 400 mg/kgBW. Further research is recommended to explore the impact of celery leaf extract on hyperglycemic conditions by comparing various parameters. Additionally, future studies should aim to identify the specific contents of celery leaf extract, elucidating the substances that play a role in cell repair and development. Conducting research in clinical settings would provide insights into the efficiency and effectiveness of using celery leaf extract as a complementary therapy for hyperglycemic conditions.

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