10. The Effect Of Red Betel Leaves (Piper Crocatum Ruiz And Pav.) On Blood Sugar And Insulin Expression Levels In Rat

by Riami Riami

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Research Article

The effect of red betel leaves (*Piper crocatum* Ruiz and Pav.) on blood sugar and insulin expression levels in rat (*Rattus norvegicus* domesticus) models of diabetes mellitus

Riami Riami[1,2]*, I Ketut Sudiana[3], Bambang Purwanto[4]

ABSTRACT

Aim: This study aimed to analyze the effect of red betel leaf extract administration on blood sugar levels and insulin expression levels of Wistar rats (*Rattus norvegicus domesticus*) as diabetic mellitus models. **Materials and Methods:** The successful diabetes mellitus (DM) male rat (grouped into K2 and K3) was treated with red betel leaf extract (50 and 100 mg/kgBW/day, respectively) for 21 days and compared to DM control (K1) and normal control (K0). Observation was fasting blood sugar level (FBS) and insulin expression with immunohistochemical analysis. **Results:** All data were analyzed for variance homogeneity using Brown–Forsythe test and continued to Games-Howell test with significance value of 5%. Based on the results of the variance homogeneity test, the FBS value and insulin expression in pancreatic β-cells were not homogeneous. The result of Games-Howell tests showed that FBS of treatment groups (K1, K2, and K3) was higher than control (K0) ($P < 0.005$). The expression of insulin in pancreatic β-cells also showed difference significantly in all groups. Expression of insulin in DM rats treated with low red betel concentration was significantly higher than high concentration (50 and 100 mg/kgBW per day, respectively). **Conclusion:** Therefore, ethanol extract from red betel leaf can reduce FBS levels and increase insulin expression in diabetic rats.

KEY WORDS: Diabetes mellitus, Fasting blood sugar levels, Insulin expression, Red betel

INTRODUCTION

The pancreas is an exocrine and endocrine gland. It has soft consistency because it contains lots of glandular tissue and it is divided into parts (caput, corpus, and cauda), weighing an average of 80 g. The pancreas endocrine function is carried out by a group of cells called the Island of Langerhans, which produces the hormones insulin that is important for carbohydrate metabolism. Cell damage in Langerhans Island which causes impaired insulin secretion can be associated with diabetes mellitus (DM).[1]

DM is associated with abnormal metabolic processes of carbohydrates, proteins, and fats, which causes chronic complications including microvascular, macrovascular, and neuropathic conditions.[2] DM sufferers are immunocompromised hosts, which are an effect that is difficult to control, this immunocompromised state will increase susceptibility, severity, and mortality in patients with DM.[3-4]

The number of DM sufferers continues to increase along with changes in lifestyle, types of food consumed, lack of physical activity, and other factors. Based on the estimation by the Diabetic Federation, there were 5.6 million people with DM in Indonesia, in 2001, and this is expected to increase to 8.2 million people by 2020, if there is no change to a healthy lifestyle for sufferers. According to a survey conducted by the WHO, the number of DM patients in Indonesia ranks fourth highest with a prevalence of 8.6% of the total population, after India, China, and the United States of America.[5] In 2013, the proportion of Indonesians aged >15 years with DM was 6.9%. The highest prevalence of DM diagnosed by doctors was in Yogyakarta (2.6%), DKI Jakarta (2.5%), North Sulawesi (2.4%), and East Kalimantan (2.3%).

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[1]Doctoral Program in Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, [2]Department of Anatomy, Faculty of Medicine, Universitas Hang Tuah, Surabaya, Indonesia, [3]Department of Pathology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia, [4]Department of Physiology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.

***Corresponding author:** Riami Riami, Doctoral Program in Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; Department of Anatomy, Faculty of Medicine, Universitas Hang Tuah, Surabaya, Indonesia. E-mail: riami@hangtuah.ac.id

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The prevalence of DM diagnosed by doctors or based on symptoms is highest in Central Sulawesi (3.7%), North Sulawesi (3.6%), South Sulawesi (3.4%), and East Nusa Tenggara (3.3%).[6]

There are two main types of DM, type 1 diabetes usually develops in childhood and adolescence, and patients need lifelong insulin injections to survive. Type 2 diabetes usually develops in adulthood and is associated with obesity, lack of physical activity, and an unhealthy diet. Type 2 diabetes is the more common type of diabetes (representing 90% of diabetes cases worldwide), and the treatment may involve lifestyle changes, weight loss, oral medications, or even insulin injections. Other types of diabetes include gestational diabetes and "other" such as rare causes (genetic syndromes and source damage such as pancreatitis, cystic fibrosis, exposure to certain drugs, viruses, and unknown causes).[7] Type 1 diabetes occurs in 5–10% of DM cases and type 2 diabetes in 90–95% of DM cases.[2] Patients with type 1 diabetes require the administration of exogenous insulin. Patients with type 2 diabetes need oral antidiabetic drugs therapy (monotherapy) or combination therapy. If the desired remediation is not achieved, it is necessary to supply exogenous insulin.[8-9]

Application of herbal medication for healing disease, especially for DM, may have alternative solution for remediation and therapy without chemical substances. Red betel (*Piper crocatum* Ruiz and Pav.), which used as an ornamental plant in the 1990s, has great potential to treat DM, besides of hypertension, leukemia, tuberculosis, ulcers, gout, and kidney stones.[10] Based on the previous study conducted by Safithri *et al*., the water of red betel leaf decoctions has efficacy as an antihyperglycemic agent at a dose of 20 mg/kg body weight (BW) and can reduce blood glucose by up to 40% over 13 days of treatment in diabetic white rats.[11] Thus, this study aimed to analyze the effect of red betel leaf extract administration on blood sugar levels and insulin expression levels of Wistar rats (*Rattus norvegicus* domesticus) as diabetic mellitus models.

MATERIALS AND METHODS

Research Design

This research was an experimental laboratory study with Post-Test Only Control Group Design conducted in the biochemistry section of the Faculty of Medicine, Airlangga University. The experimental animal in this study was adult male Wistar strain rats (*R. norvegicus* domesticus) aged 60–70 days with a BW of 150–200 g, with good health. Experimental animals were given standard feed and drink *ad libitum*. The minimum sample size used was five rats for each treatment group. The total sample size was 20 rats. The number of samples or experimental units in this study uses the large sample formula from Lwanga and Lameslaw.[12]

Red Betel Extraction

The red betel leaves (*P. crocatum* Ruiz and Pav.) were obtained from UPT Materia Medica (Batu Regency, East Java), and the ethanol extraction was carried out at the Pharmacy Laboratory of Widya Mandala University, Surabaya. The red betel leaf was thinly sliced and dried for a week in an open place with good air circulation and not exposed to direct sunlight. Dried red betel leaves (100 g) were crushed into a dry powder using a blender. The red betel leaf powder was soaked with 70% ethanol, with a ratio of 1:10 (w/w), for 3 days. The ethanol solution was filtered with filter paper to remove the leaf residue. Then, the obtained filtrate was evaporated with a vacuum rotary evaporator to get a red betel leaf extract paste. The extract was then evaporated again with a freeze dryer to obtain the dry extract. Then, 2 mg of the dry red betel extract was mixed with distilled water until the volume reached 100 mL (2% concentration of red betel leaf extract).

Treatment Groups

A total of 20 male rats aged 60–70 days with the BW of 150–200 g were randomly divided into four groups (K0, K1, K2, and K3). Wistar rats for K1, K2, and K3 with criteria above were injected with streptozotocin (Sigma, St. Louis, MO, USA) with a dose of 50 mg/kgBW to created DM Wistar rats. Positive DM Wistar rats were indicated by fasting blood sugar (FBS) level in 48 h after injection is above 14 mmol/L or 252 mg/dL and accompanied by polyphagia, polydipsia, polyuria, and weight loss.[13]

For treatment, the K0 or normal control group was treated with normal saline, the K1 or DM control group was treated with normal saline, the K2 or DM group was treated with red betel leaf extract 50 mg/kgBW/day, and the K3 or DM group was treated with red betel leaf extract 100 mg/kgBW/day.

FBS Measurement

The blood glucose was measured using a glucometer (Optium Xceed, MediSense, Almada, USA). The glucometer was adjusted and settled according to the glucose stick code used, and then, the blood sample that was taken from the tail was dripped onto the stick connected to the glucometer.

Pancreas Slides Preparation

The rats were euthanized intramuscularly by ketamine and dissection of rats was performed to collect the pancreatic organ. The pancreas organ was embedded in a paraffin block, which was fixed in the microtome block holder and arranged parallel to the microtome blade. The pancreas organ was sliced to a size of 5 µm. The slices were taken by brush and put on the surface of room

temperature water to open the folds that might occur during the preparation. Then, the slices were transferred with a brush into warm water (38–40°C) to straighten any possible wrinkles. A perfectly stretched slice was taken with a glass slide. The glass slides were placed on a 38–40°C hot plate until dry, and then, the glass slides were stored in an incubator at 38–40°C for 24 h.

Immunohistochemical (IHC) Analysis

The pancreas organ slices that had been fixed in the glass slides were deparaffinized and rehydrated with xylol (I, II, and III) and 90, 80, and 70% ethanol. Furthermore, the pancreas prepared slides were washed with phosphate buffer solution (PBS) at pH 7.4, and then, the endogenous peroxidase was blocked with 3% H_2O_2 in distilled water for 30 min and washed with PBS 3 times for 5 min. Ultra V Block was applied to the slide for 5 min along with goat serum added with anti-insulin primary antibody (1:300) and then incubated overnight in the refrigerator. The slides were then washed with PBS at pH 7.4 for 5 min 3 times before diaminobenzidine (DAB) was applied. The pancreas prepared slide was then rinsed with 3% H_2O_2 for 10 min and washed with PBS at pH 7.4.

The secondary antibodies biotinylated goat anti-polyvalent was applied for 10 min and then washed with PBS. The streptavidin-peroxidase enzyme conjugate was added and incubated for 10 min, then washed with PBS. The substrate and chromogen of 3,3'-DAB was applied then incubated for 10 min at room temperature in the dark. The slides were washed with distilled water and counterstained with hematoxylin for 10 s, then washed with running water and distilled water. Finally, the slides were dehydrated with multilevel ethanol, cleared with xylol, and mounted with Canada balsam (Novusbio K36Ac10/NB600-1488).

Pancreas prepared slides were observed under the microscope. The insulin expression was examined and calculated from the brown color in the cytoplasm of cells. Each slide in the field of view was observed using 400× magnifications in 10 fields of view/Langerhans Island.

Data Analysis

All data from FBS level and insulin expression were tested for homogeneity using Brown–Forsythe test with significance of 5%. Then, the Games-Howell test was carried out to find out which groups were different.

RESULTS

FBS level

Based on Brown–Forsythe test, all groups' data were not homogeneous ($P = 0.003$; $P < 0.05$) and continued to Games-Howell non-parametric test. Then, the result showed that FBS level in treatment groups (K1, K2, and K3) was significantly higher compared to control (K0). The lowest FBS level in treatment groups was observed at K2 with the value of 399.8 ± 115.56 mg/dL. However, that value was insignificant based on Games-Howell non-parametric test [Figure 1].

Insulin Expression Level

Figure 2 shows the pancreas tissue observation with IHC staining. The group with streptozotocin (STZ) induction (K1) expressed a small amount of insulin, shown by the low levels of insulin and anti-insulin positive reaction in the β-cells. STZ injection causes damage to the DNA of β-cells, which leads to low insulin expression so that the insulin hormone detected by IHC staining is also low. The IHC result of K1 clearly shows that the high damage of the β-cell causes the cell to be unable to produce insulin.

The results of the insulin variant homogeneity test showed that all groups' data were not homogeneous based on Brown–Forsythe test. Then, the result showed insulin expression level between control and treatment groups and among three treatment groups showed different significantly. The highest insulin expression level was in control group, about

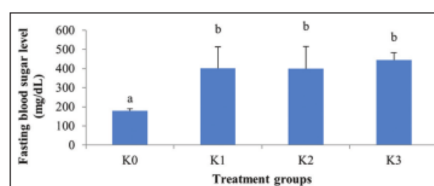

Figure 1: The fasting blood sugar level in each group. Two bars followed by same letter indicate insignificantly different based on Games-Howell test for 5%

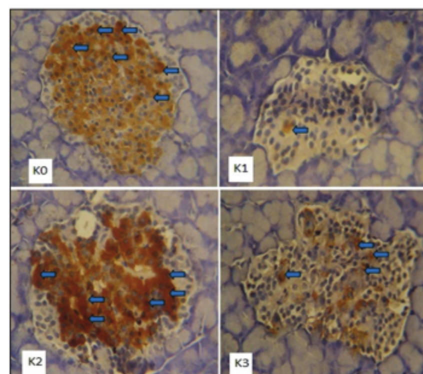

Figure 2: Rat pancreatic β-cell insulin expression (*Rattus norvegicus*) with Immunohistochemical staining and 400× magnification. The arrow shows the pancreatic β-cells that express insulin

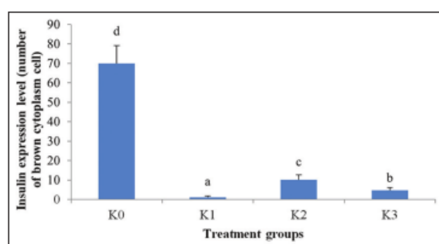

Figure 3: Insulin expression level in each group. Two bars followed by same letter indicate insignificantly different based on Games-Howell test for 5%

7–70 times higher than treatment groups. In treatment groups, red betel extract treatment (K2 and K3) has higher insulin expression than DM control group (K0) [Figure 1]. However, the highest concentration of red betel extract (50 mg/kgBW per day) has a low level of insulin expression compared to low concentration (50 mg/kgBW per day) [Figure 3].

DISCUSSION

The final results showed that there were differences in the average blood sugar levels in the four groups, with the lowest blood sugar level being found in the K0 group (179 mg/dL), which was not given red betel extract and used as a negative control (no DM Wistar rats). Whereas average of FBS levels in K1 or the positive control was increased, which was 402.20 mg/dL, this may be due to the effect of STZ, which caused rats to be hyperglycemic with no treatment of red betel extract. In the K2 group, there was a slight decrease in the average blood sugar level (399.80 mg/dL) after being given 50 mg/kgBW red betel extract. This was consistent with previous research conducted by Liestiono *et al.* and Sinu.[14-15] They suggested that application of red betel could improve regeneration of beta-pancreatic cells which contribute in decreasing FBS level. Red betel contains chemical compounds that can lower blood sugar levels, namely flavonoids, alkaloids, and tannins. In the previous studies, it has been observed that flavonoids activate inhibitors of α-glucokinase, one of the catalysts that promote the carbohydrate hydrolysis to glucose in the intestine.[16] Flavonoids also stimulate the β-cells, causing increased insulin secretion, and consequently lowering blood sugar levels. It also activates the peroxisome proliferator-activated receptors.[17]

The analysis of pancreas tissue stained with antibodies to insulin was done by calculating the expression of pancreatic β-cells that are immunoreactive to insulin and appear brown. The reduced insulin expression of pancreatic β-cells that are immunoreactive against insulin antibodies indicates a decrease in insulin synthesis.[18] In this research, the administration of 50 mg/kgBW (K2) of the red betel extract [Figure 3] was able to repair the damage of pancreatic β-cells due to STZ induction. In the K2 group, the results showed improving pancreatic β-cells function compared to the administration of 100 mg/kgBW (K3) red betel extract. The quercetin found in flavonoids can reduce oxidative stress and prevent damage on pancreatic β cells in diabetic rats, which is induced by STZ.[19]

The dose of 50 mg/kgBW of red betel extract is the optimum dose that is able to repair the damage of pancreatic β-cells and could lead to an increase in the insulin expression; however, it is not the highest in reducing blood sugar levels. The higher dose of 100 mg/kgBW was able to repair the damage of β pancreas cells so that it lowers the FBS levels, but not as much as the dose of 50 mg/kgBW. This difference might be due to the dose of red betel extract containing antioxidants, which affects the oxidation rate. At high concentrations, antioxidant activity often vanishes or can even turn into pro-oxidants, which means that the antioxidant function is no longer available. This result is consistent with the theory that states the rate of oxidation is influenced by the antioxidant concentration. At high concentrations, antioxidant activity often disappears and even these antioxidants will become pro-antioxidants.[20]

In line with the previous studies, in diabetic rats that were given the same dose of STZ and treated with quercetin flavonoid (15 mg/kgBW/day) for 4 weeks, the results of insulin expression were improved. Quercetin flavonoids not only protect pancreatic β-cells but they can also increase insulin sensitivity by reducing oxidative stress. Decreased cell damage of β pancreas cells will increase insulin secretion and consequently decrease blood sugar levels in diabetic rats.[19]

CONCLUSION

In summary, red betel ethanol extract may improve the function of beta pancreatic cells damage.

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